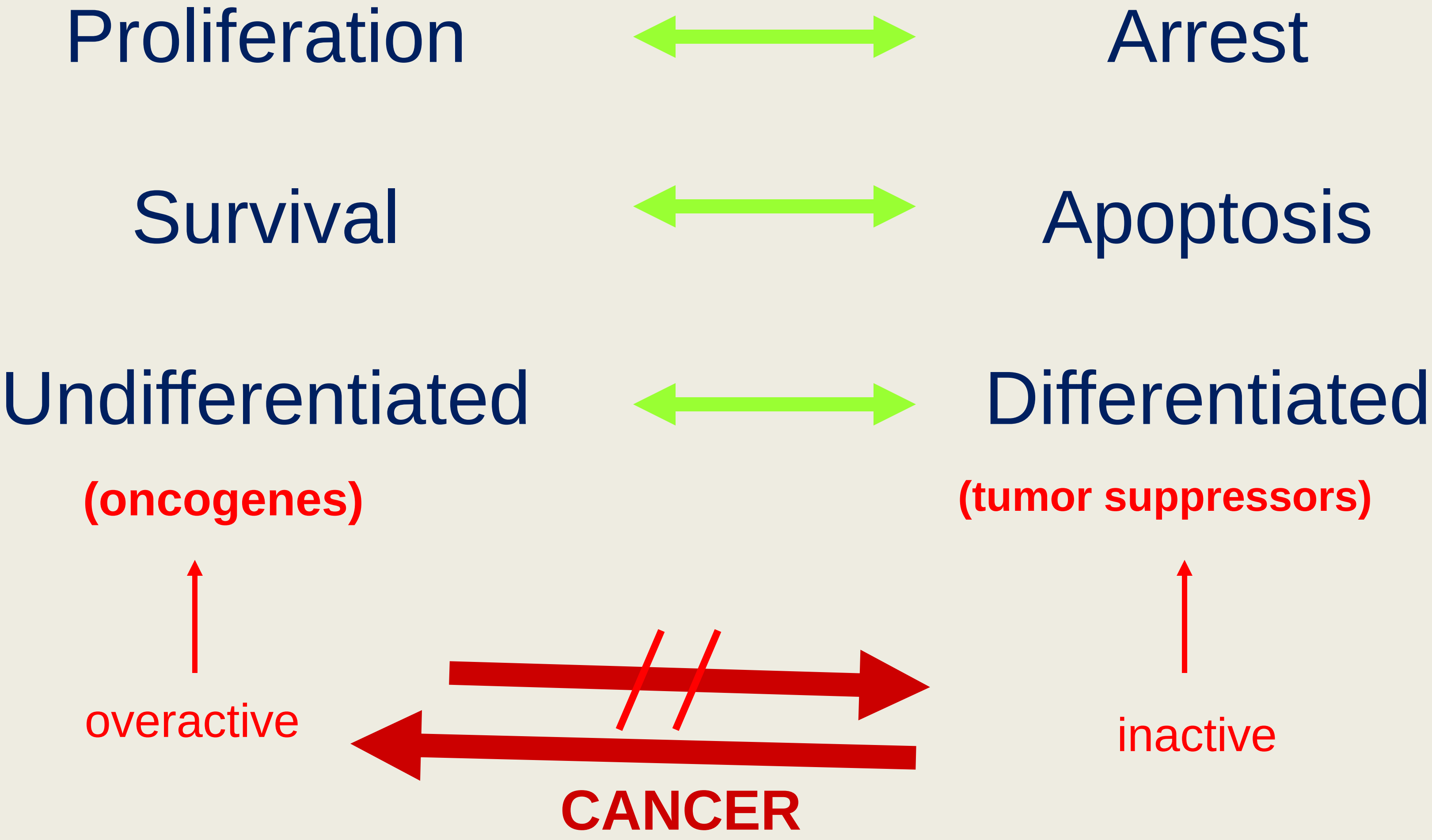
Cellular homeostasis



Proliferation ⟷ Arrest

Survival ⟷ Apoptosis

Undifferentiated ⟷ Differentiated

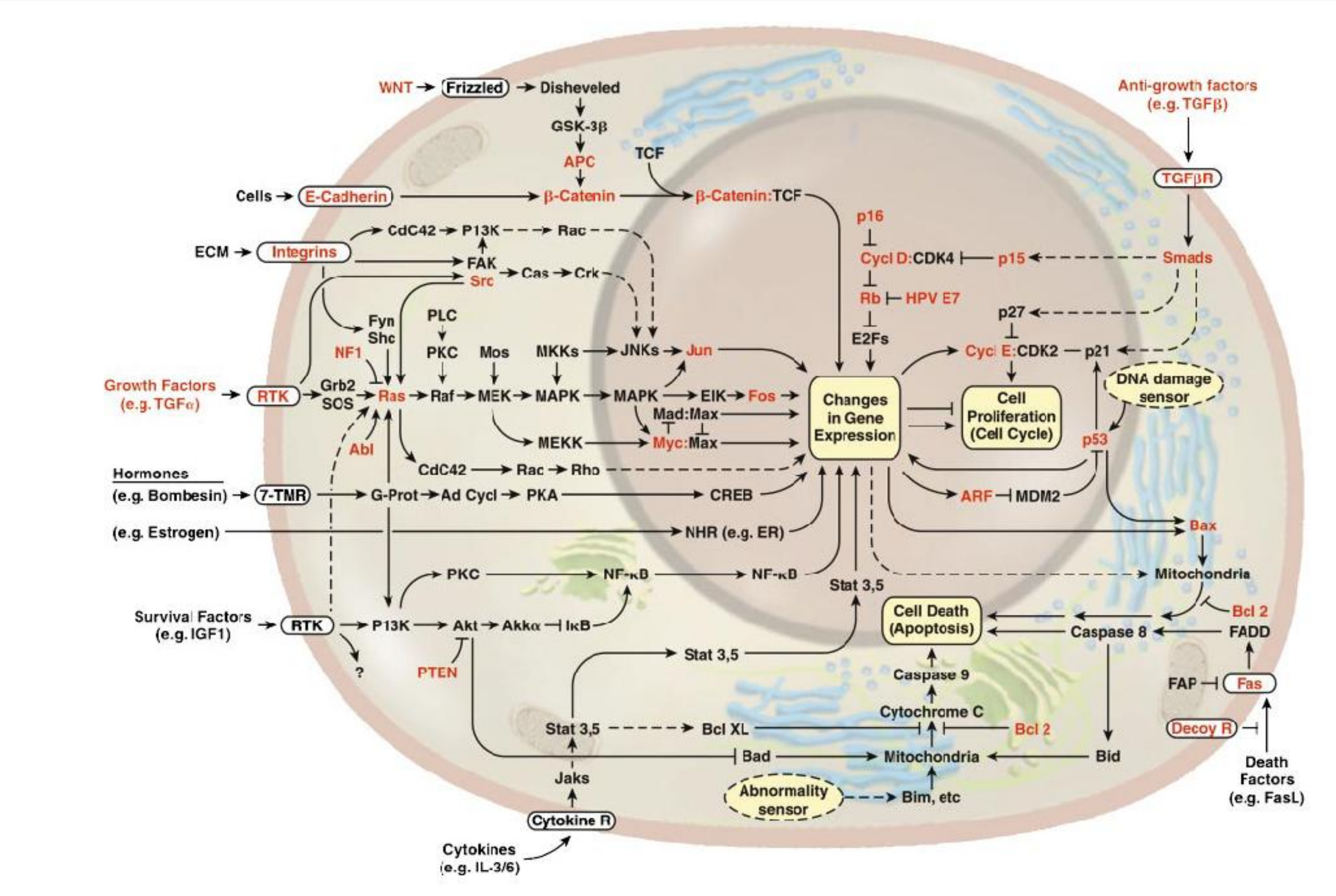
(oncogenes)

(tumor suppressors)

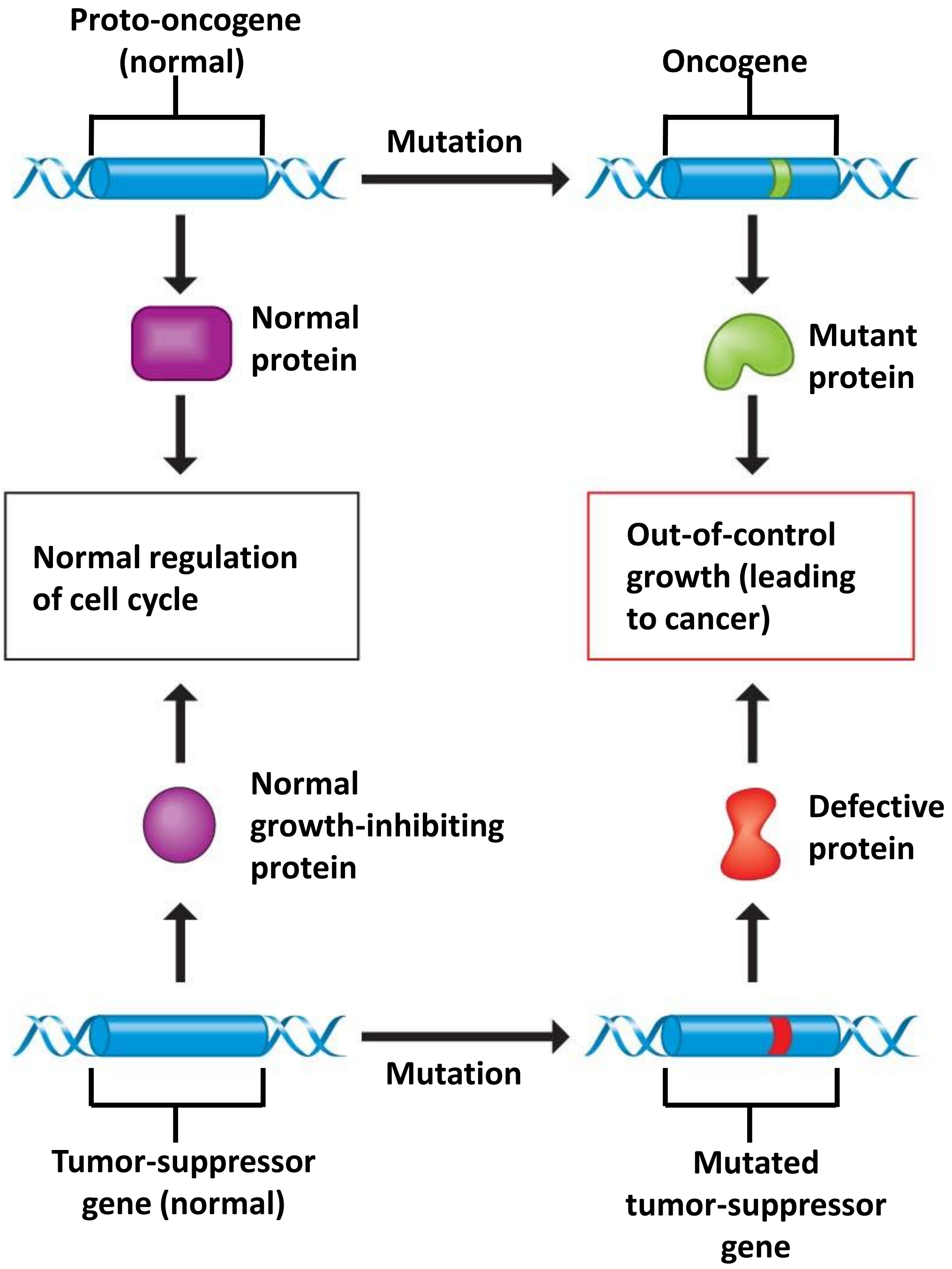
overactive

inactive

CANCER



CANCER IS CAUSED BY THE BREAKDOWN OF SEVERAL IMPORTANT NETWORKS,THAT GUARD AGAINST UNCONTROLLED PROLIFERATION


Proto-oncogene (normal)
Mutation
Oncogene
Normal protein
Mutant protein
Normal regulation of cell cycle
Out-of-control growth (leading to cancer)
Normal growth-inhibiting protein
Defective protein
Mutation
Tumor-suppressor gene (normal)
Mutated tumor-suppressor gene

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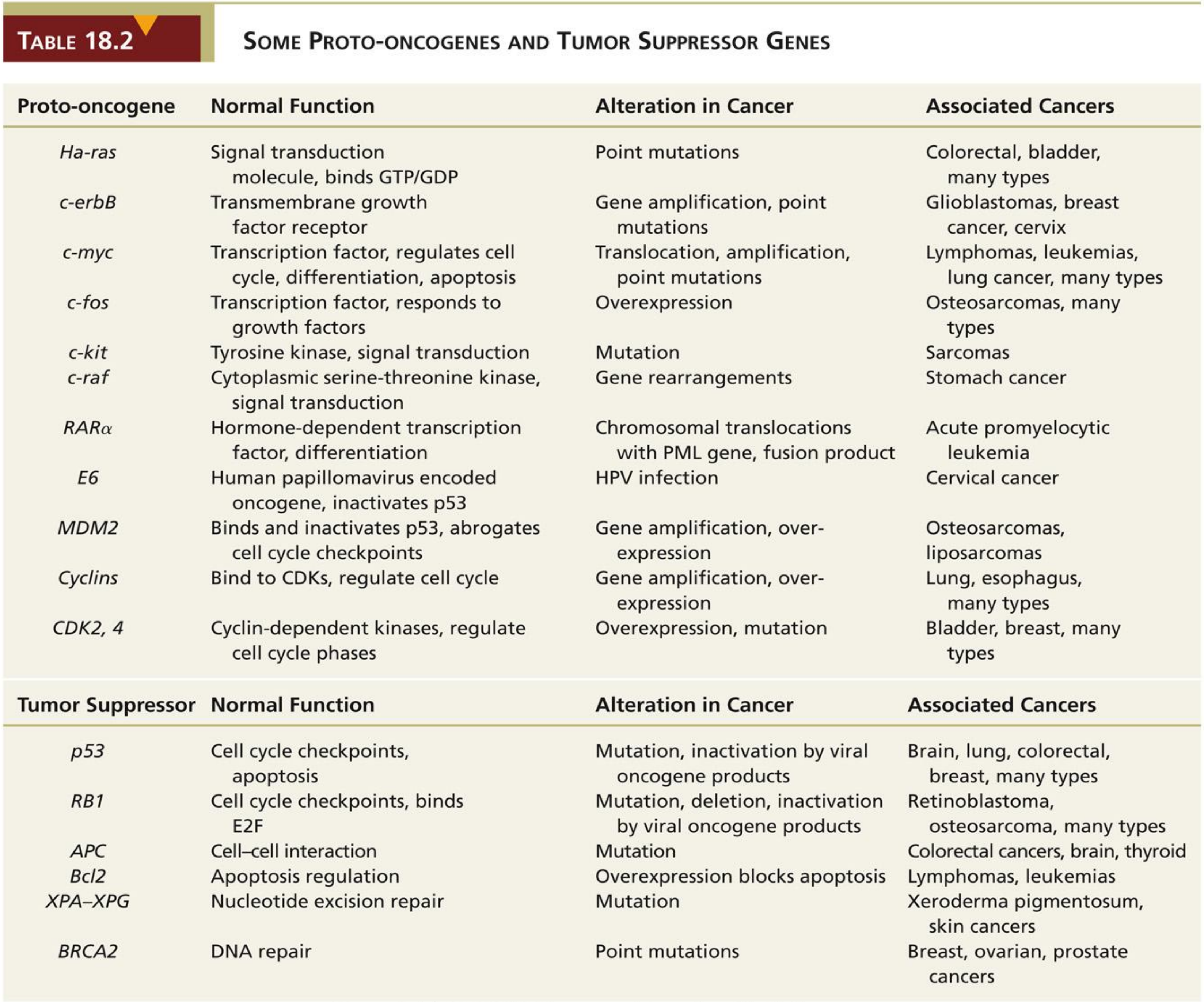

Table 18.2 Some Proto-oncogenes and Tumor Suppressor Genes

Proto-oncogene	Normal Function	Alteration in Cancer	Associated Cancers
Ha-ras	Signal transduction molecule, binds GTP/GDP	Point mutations	Colorectal, bladder, many types
c-erbB	Transmembrane growth factor receptor	Gene amplification, point mutations	Glioblastomas, breast cancer, cervix
c-myc	Transcription factor, regulates cell cycle, differentiation, apoptosis	Translocation, amplification, point mutations	Lymphomas, leukemias, lung cancer, many types
c-fos	Transcription factor, responds to growth factors	Overexpression	Osteosarcomas, many types
c-kit	Tyrosine kinase, signal transduction	Mutation	Sarcomas
c-raf	Cytoplasmic serine-threonine kinase, signal transduction	Gene rearrangements	Stomach cancer
RARα	Hormone-dependent transcription factor, differentiation	Chromosomal translocations with PML gene, fusion product	Acute promyelocytic leukemia
E6	Human papillomavirus encoded oncogene, inactivates p53	HPV infection	Cervical cancer
MDM2	Binds and inactivates p53, abrogates cell cycle checkpoints	Gene amplification, overexpression	Osteosarcomas, liposarcomas
Cyclins	Bind to CDKs, regulate cell cycle	Gene amplification, overexpression	Lung, esophagus, many types
CDK2, 4	Cyclin-dependent kinases, regulate cell cycle phases	Overexpression, mutation	Bladder, breast, many types

Tumor Suppressor	Normal Function	Alteration in Cancer	Associated Cancers
p53	Cell cycle checkpoints, apoptosis	Mutation, inactivation by viral oncogene products	Brain, lung, colorectal, breast, many types
RB1	Cell cycle checkpoints, binds E2F	Mutation, deletion, inactivation by viral oncogene products	Retinoblastoma, osteosarcoma, many types
APC	Cell–cell interaction	Mutation	Colorectal cancers, brain, thyroid
Bcl2	Apoptosis regulation	Overexpression blocks apoptosis	Lymphomas, leukemias
XPA–XPG	Nucleotide excision repair	Mutation	Xeroderma pigmentosum, skin cancers
BRCA2	DNA repair	Point mutations	Breast, ovarian, prostate cancers

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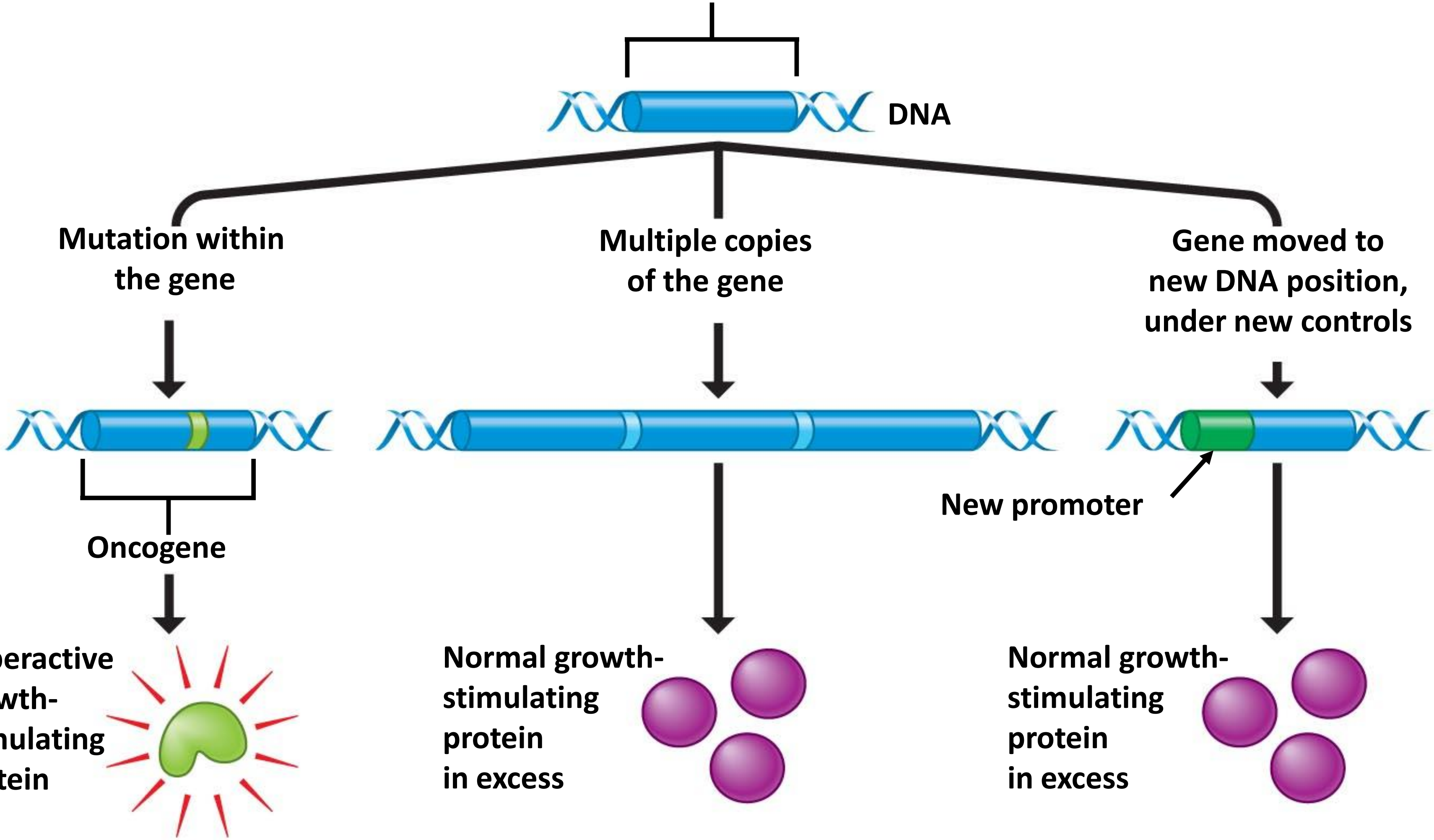
Definitions

- Oncogene – a gene that when mutated or expressed at abnormally high levels contributes to converting a normal cell into a cancer cell
- Proto-oncogene – the “normal” cellular progenitors of oncogenes that function to promote the normal growth and division of cells

Oncogenes and Tumor-Suppressor Genes

- **Proto-oncogenes** are
  - Normal genes with the potential to become oncogenes
  - Found in many animals
  - Often genes that code for growth factors, proteins that stimulate cell division
  - For a proto-oncogene to become an oncogene, a mutation must occur in the cell's DNA.
  - **Proto-oncogenes** are at the end of a *stimulatory pathway* from the plasma membrane to the nucleus; a growth factor binding at the plasma membrane can result in turning on an oncogene. **oncogenes** (cancer-causing genes).



Proto-oncogene
(for protein that stimulates cell division)

DNA

Mutation within the gene

Multiple copies of the gene

Gene moved to new DNA position, under new controls

Oncogene

New promoter

Hyperactive growth-stimulating protein

Normal growth-stimulating protein in excess

Normal growth-stimulating protein in excess

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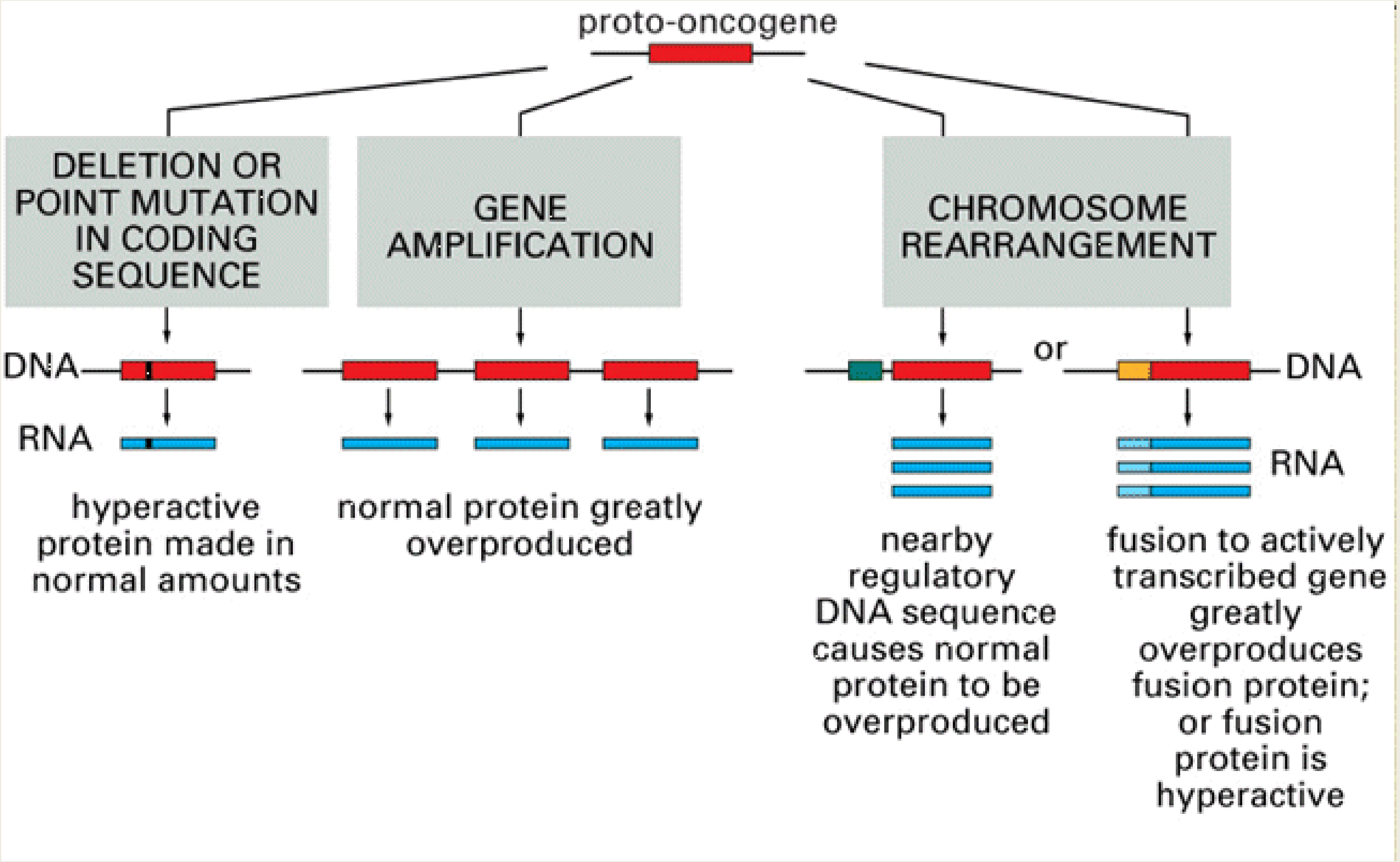
Oncogenes by function

- Growth factors
- Growth factor receptors
- G proteins
- Intracellular kinases
- Transcription factors

Proto-oncogene activation



proto-oncogene

DELETION OR POINT MUTATION IN CODING SEQUENCE

GENE AMPLIFICATION

CHROMOSOME REARRANGEMENT

hyperactive protein made in normal amounts

normal protein greatly overproduced

nearby regulatory DNA sequence causes normal protein to be overproduced

fusion to actively transcribed gene greatly overproduces fusion protein; or fusion protein is hyperactive

Types of proto-oncogene

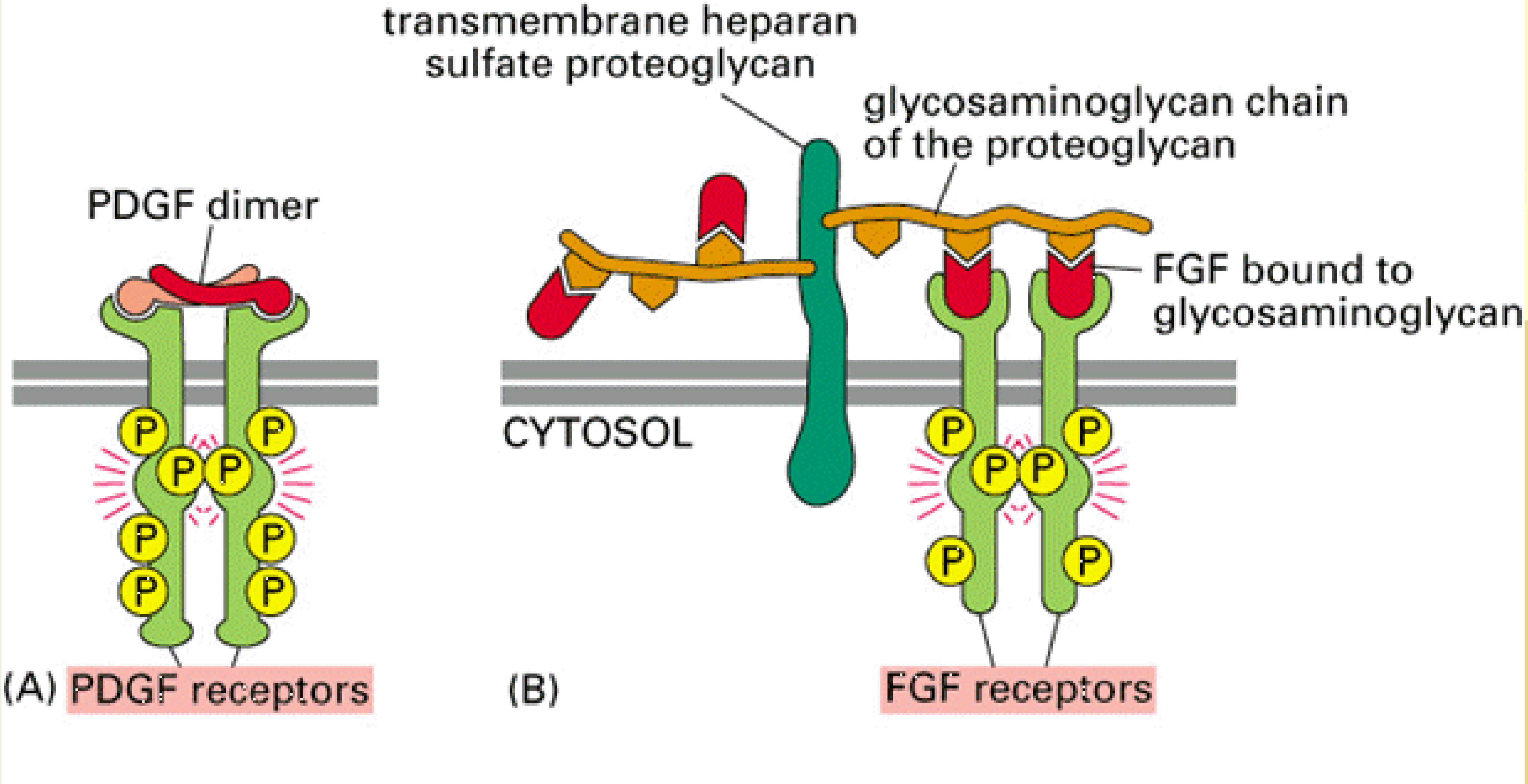
- Nuclear transcription factors
  e.g. MYC

Types of proto-oncogene

- Growth factor
  e.g. SIS oncogene (PDGF)

Types of proto-oncogene

- Growth factor receptor
  e.g. tyrosine kinase receptors


transmembrane heparan sulfate proteoglycan
glycosaminoglycan chain of the proteoglycan
PDGF dimer
FGF bound to glycosaminoglycan
CYTOSOL
P
(A) PDGF receptors
(B)
FGF receptors

Growth factor expression

- Controlled at the level of gene expression
  - Autocrine
    - Cell produces a growth factor to which it also responds
    - Sis – encodes a variant form of PDGF
      - Astrocytomas
      - Increases cell growth
  - Paracrine
    - VEGF
    - Increases growth of endothelial cells
    - Secreted by tumor

Growth Factors

Factor	**Principal Source**	**Primary Activity**	**Comments**
PDGF	platelets, endothelial cells, placenta	promotes proliferation of connective tissue, glial and smooth muscle cells	two different protein chains form 3 distinct dimer forms; AA, AB and BB
EGF	submaxillary gland, Brunners gland	promotes proliferation of mesenchymal, glial and epithelial cells	
TGF-α	common in transformed cells	may be important for normal wound healing	related to EGF
FGF	wide range of cells; protein is associated with the ECM	promotes proliferation of many cells; inhibits some stem cells; induces mesoderm to form in early embryos	at least 19 family members, 4 distinct receptors
NGF		promotes neurite outgrowth and neural cell survival	related proteins first identified as protooncogenes; trkA (***trackA***), trkB, trkC
Erythropoietin	kidney	promotes proliferation and differentiation of erythrocytes	
TGF-β	activated TH_1 cells (T-helper) and natural killer (NK) cells	anti-inflammatory (suppresses cytokine production and class II MHC expression), promotes wound healing, inhibits macrophage and lymphocyte proliferation	at least 100 different family members
IGF-I	primarily liver	promotes proliferation of many cell types	related to IGF-II and proinsulin, also called Somatomedin C
IGF-II	variety of cells	promotes proliferation of many cell types primarily of fetal origin	related to IGF-I and proinsulin

Growth Factor Receptors

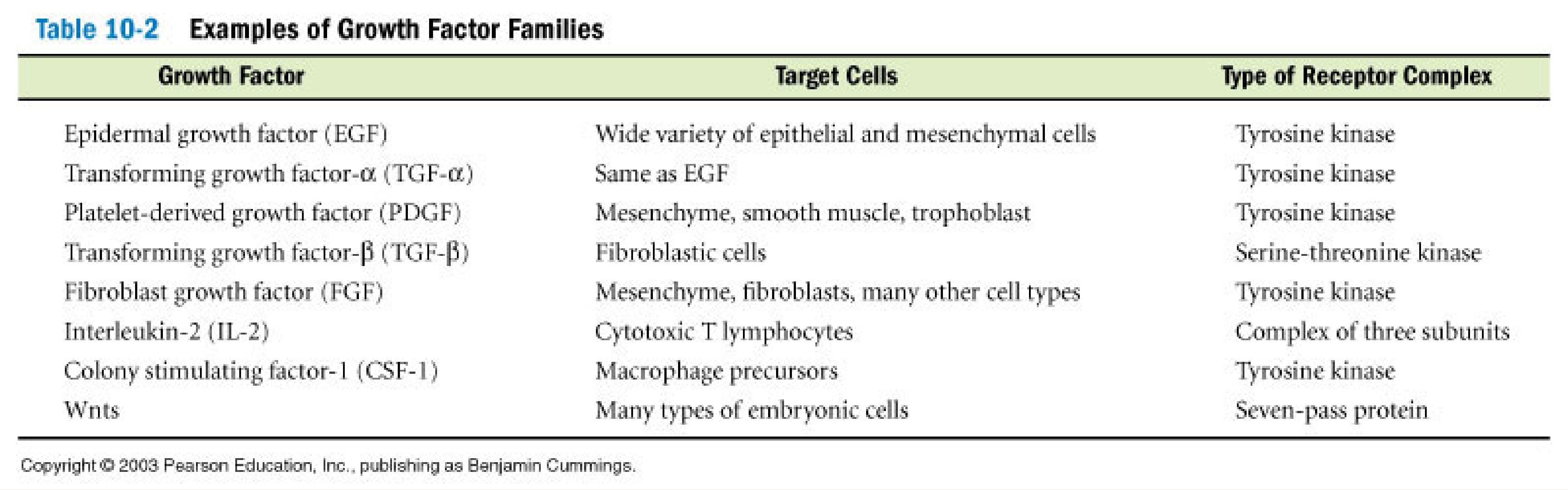


Table 10-2 Examples of Growth Factor Families

Growth Factor	Target Cells	Type of Receptor Complex
Epidermal growth factor (EGF)	Wide variety of epithelial and mesenchymal cells	Tyrosine kinase
Transforming growth factor-α (TGF-α)	Same as EGF	Tyrosine kinase
Platelet-derived growth factor (PDGF)	Mesenchyme, smooth muscle, trophoblast	Tyrosine kinase
Transforming growth factor-β (TGF-β)	Fibroblastic cells	Serine-threonine kinase
Fibroblast growth factor (FGF)	Mesenchyme, fibroblasts, many other cell types	Tyrosine kinase
Interleukin-2 (IL-2)	Cytotoxic T lymphocytes	Complex of three subunits
Colony stimulating factor-1 (CSF-1)	Macrophage precursors	Tyrosine kinase
Wnts	Many types of embryonic cells	Seven-pass protein

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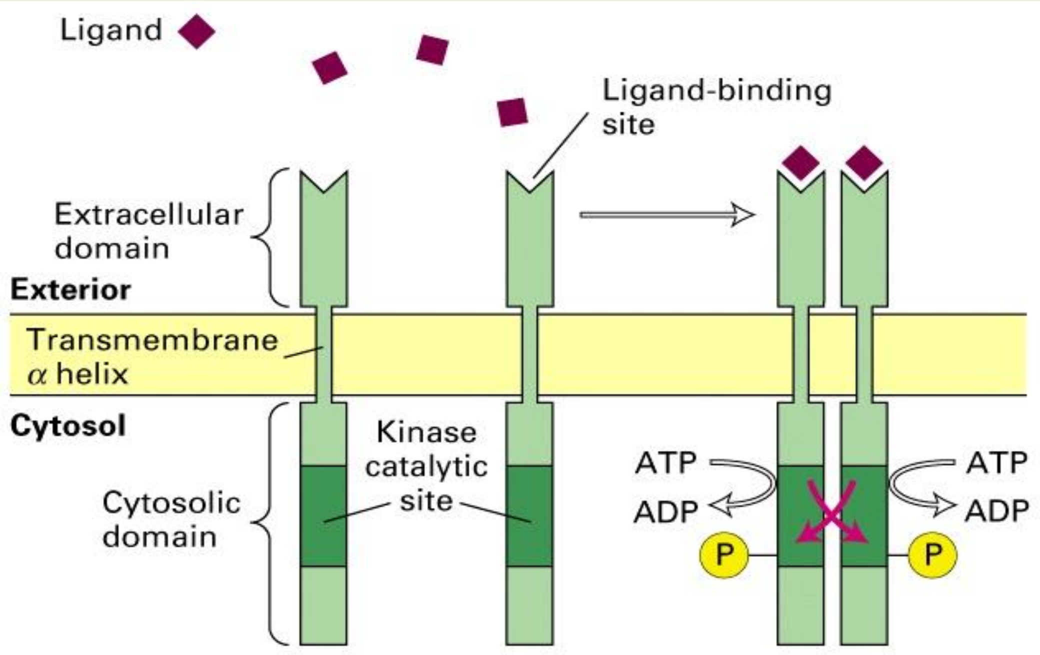

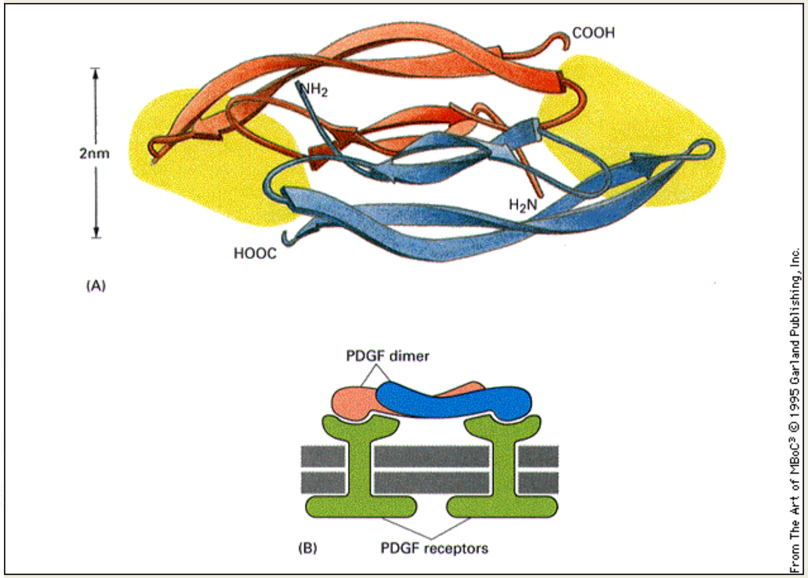

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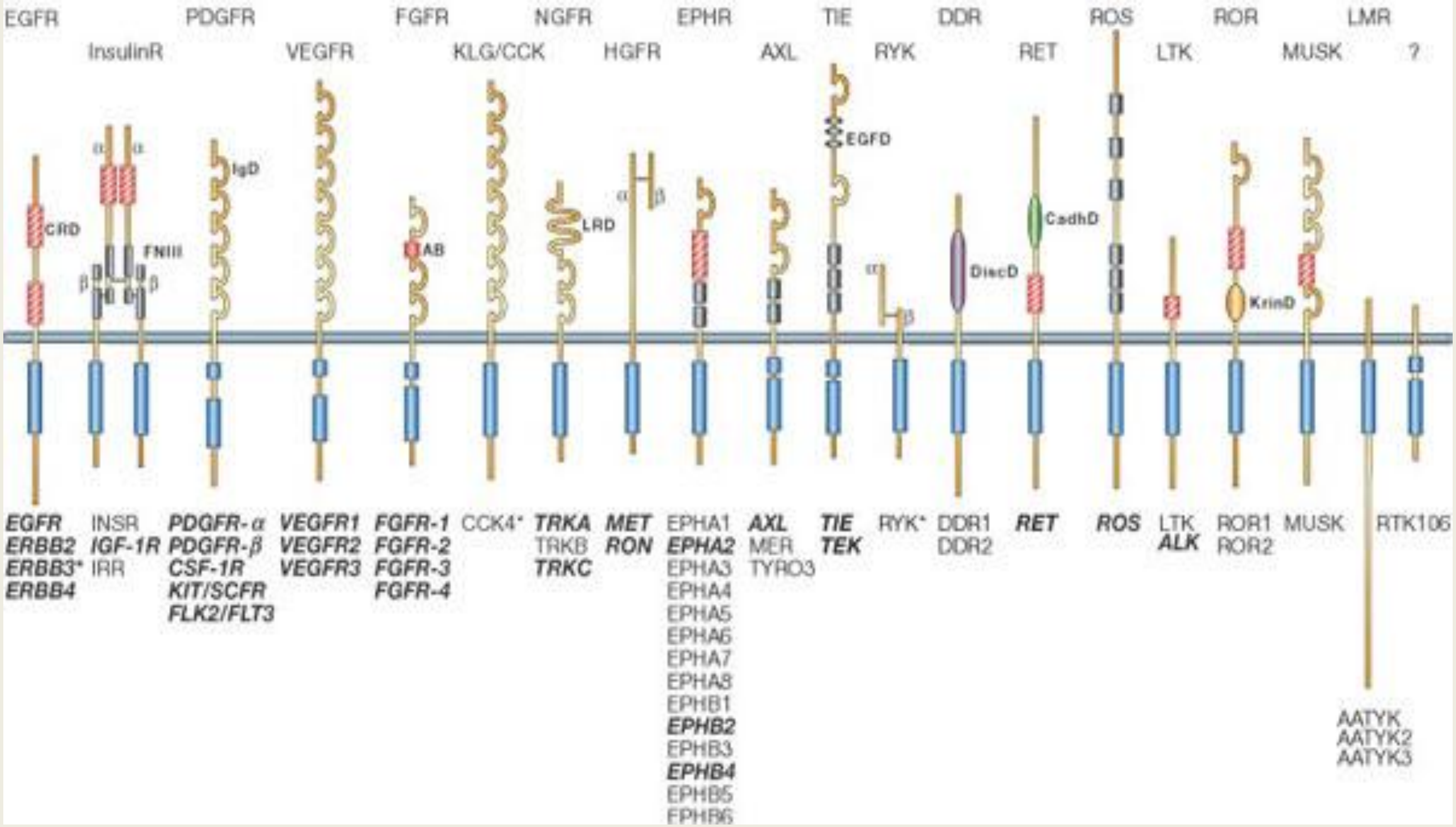
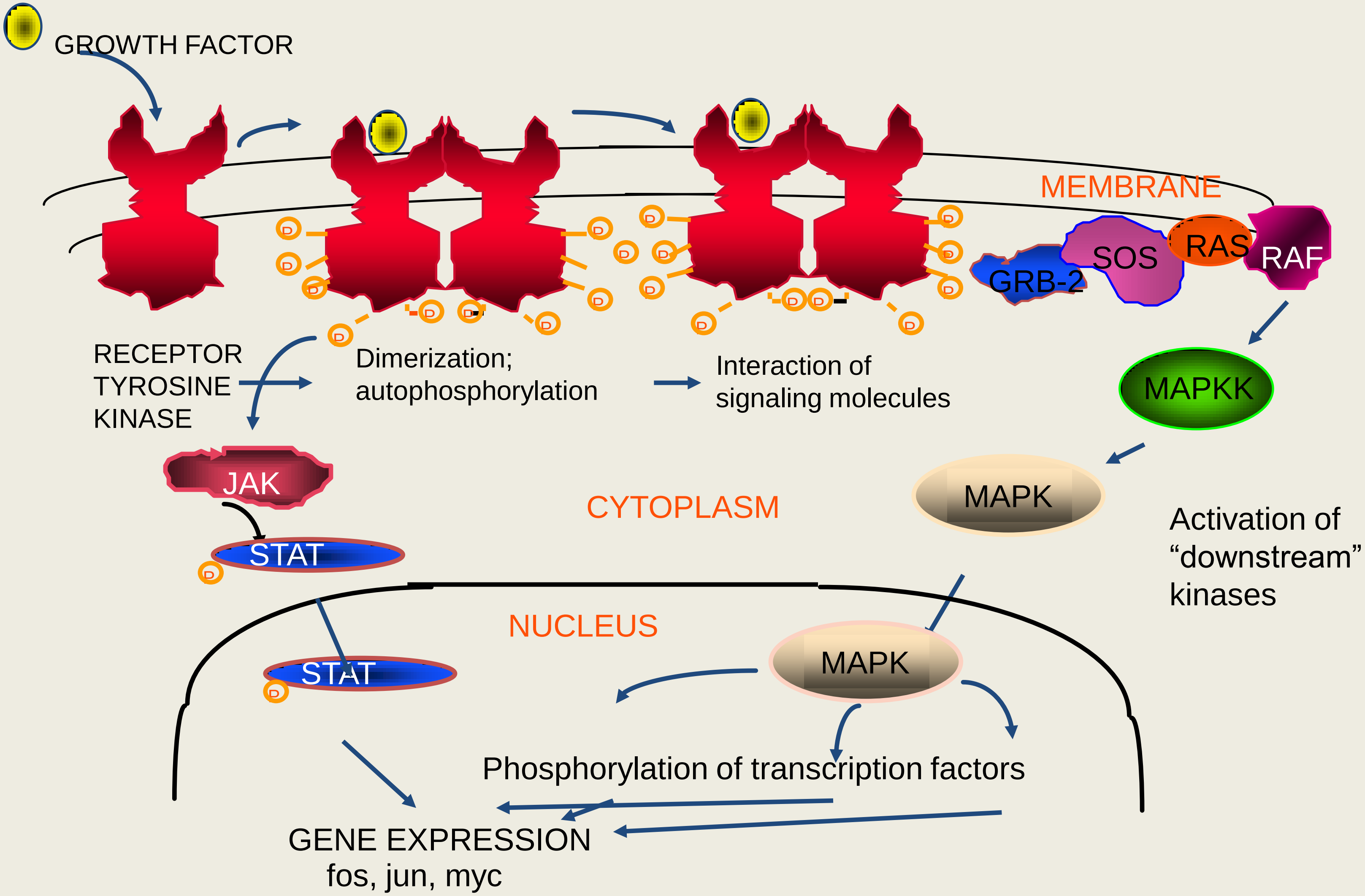
Most growth factors bind Receptor Tyrosine Kinases



SIGNAL TRANSDUCTION



GROWTH FACTOR

MEMBRANE

RECEPTOR
TYROSINE
KINASE

Dimerization;
autophosphorylation

Interaction of
signaling molecules

GRB-2

SOS

RAS

RAF

MAPKK

MAPK

Activation of
“downstream”
kinases

JAK

STAT

CYTOPLASM

NUCLEUS

STAT

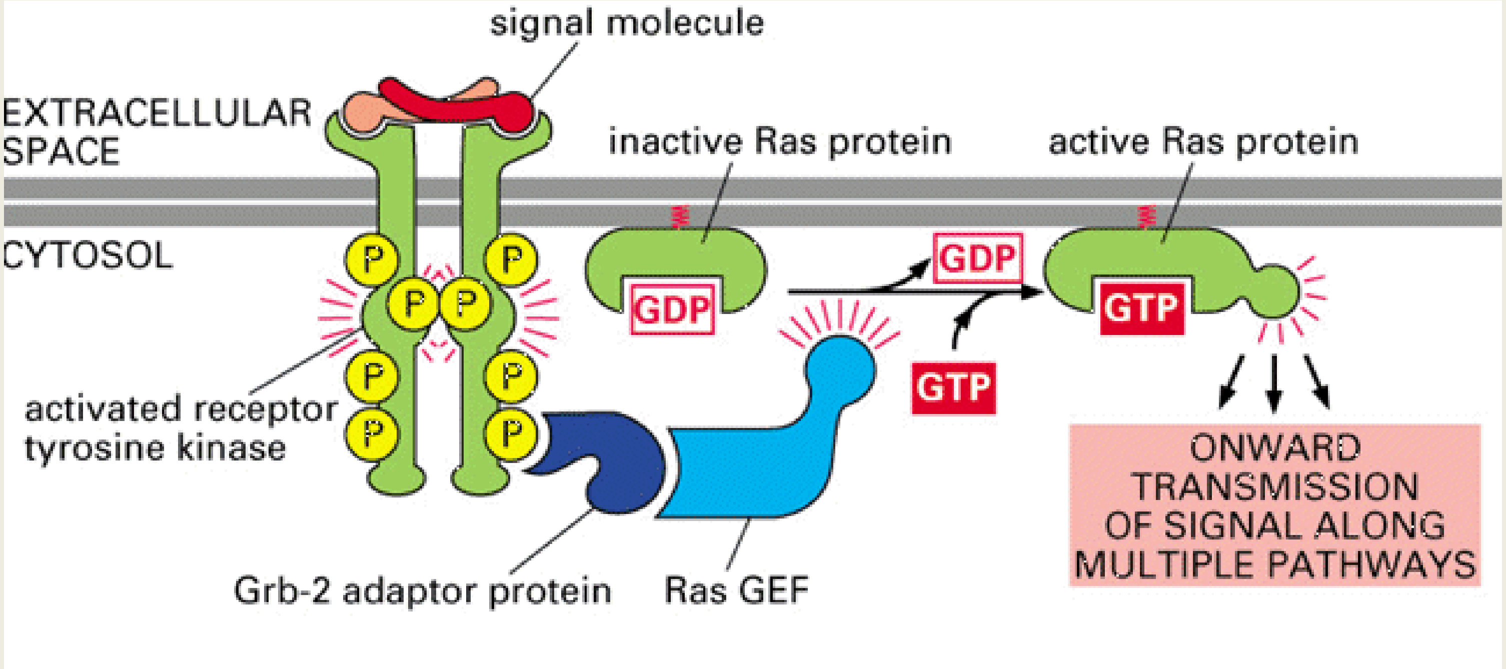
MAPK

Phosphorylation of transcription factors

GENE EXPRESSION
fos, jun, myc

Types of proto-oncogene

- G proteins
  e.g. ras

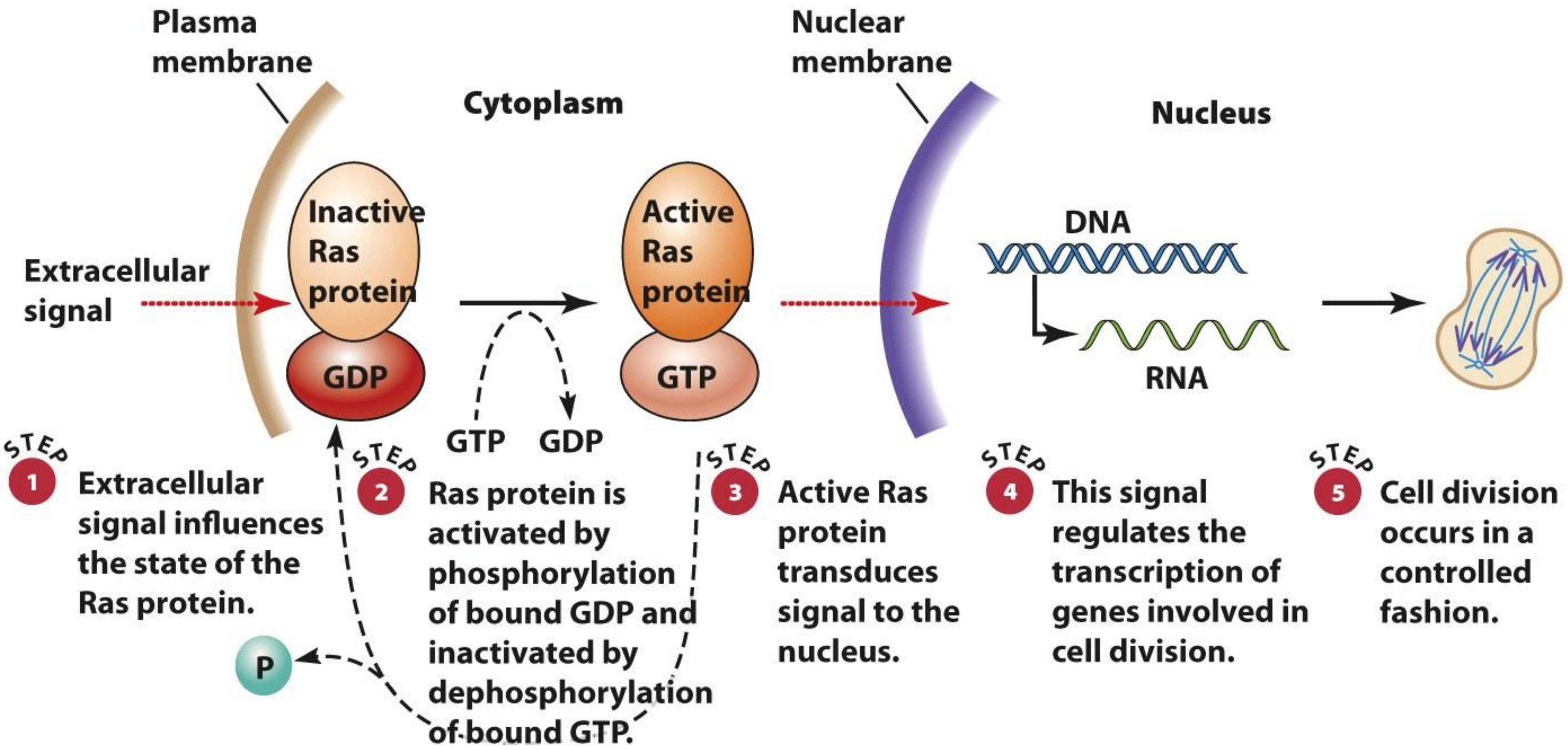


ras Proto-oncogenes

- Involved in signal transduction pathway
  - As are many proto-oncogene products
- *ras* family genes mutated in 40% of all cancers
- Involved in signal transduction pathway from growth factor receptor to nucleus
  - G protein
  - Mutant form lacks GTPase activity and remains active

Normal Ras Protein Signaling

Normal Ras protein is regulated



1 Extracellular signal influences the state of the Ras protein.

2 Ras protein is activated by phosphorylation of bound GDP and inactivated by dephosphorylation of bound GTP.

3 Active Ras protein transduces signal to the nucleus.

4 This signal regulates the transcription of genes involved in cell division.

5 Cell division occurs in a controlled fashion.

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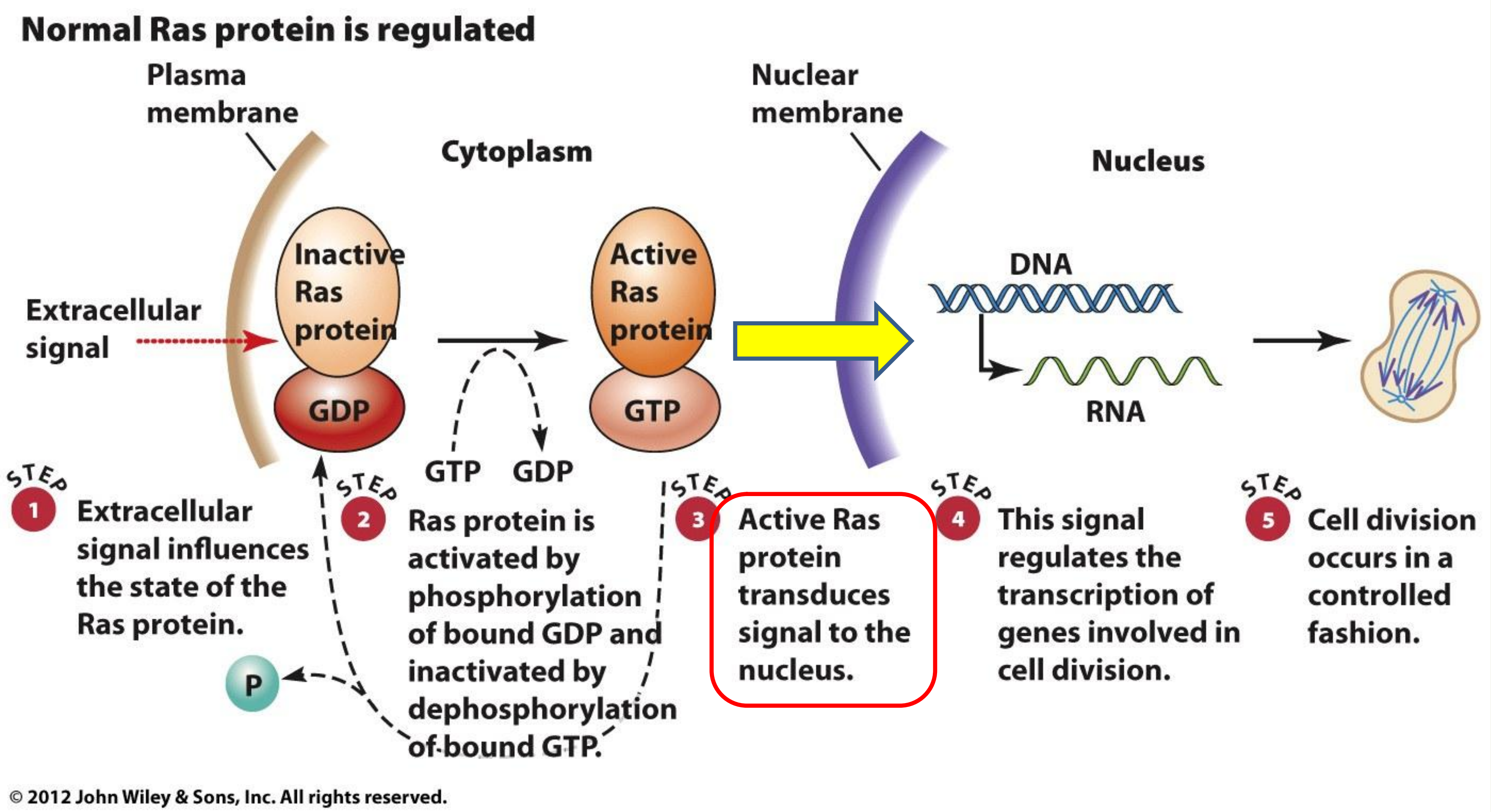
Normal Ras Protein Signaling



Normal Ras protein is regulated

① Extracellular signal influences the state of the Ras protein.

② Ras protein is activated by phosphorylation of bound GDP and inactivated by dephosphorylation of bound GTP.

③ Active Ras protein transduces signal to the nucleus.

④ This signal regulates the transcription of genes involved in cell division.

⑤ Cell division occurs in a controlled fashion.

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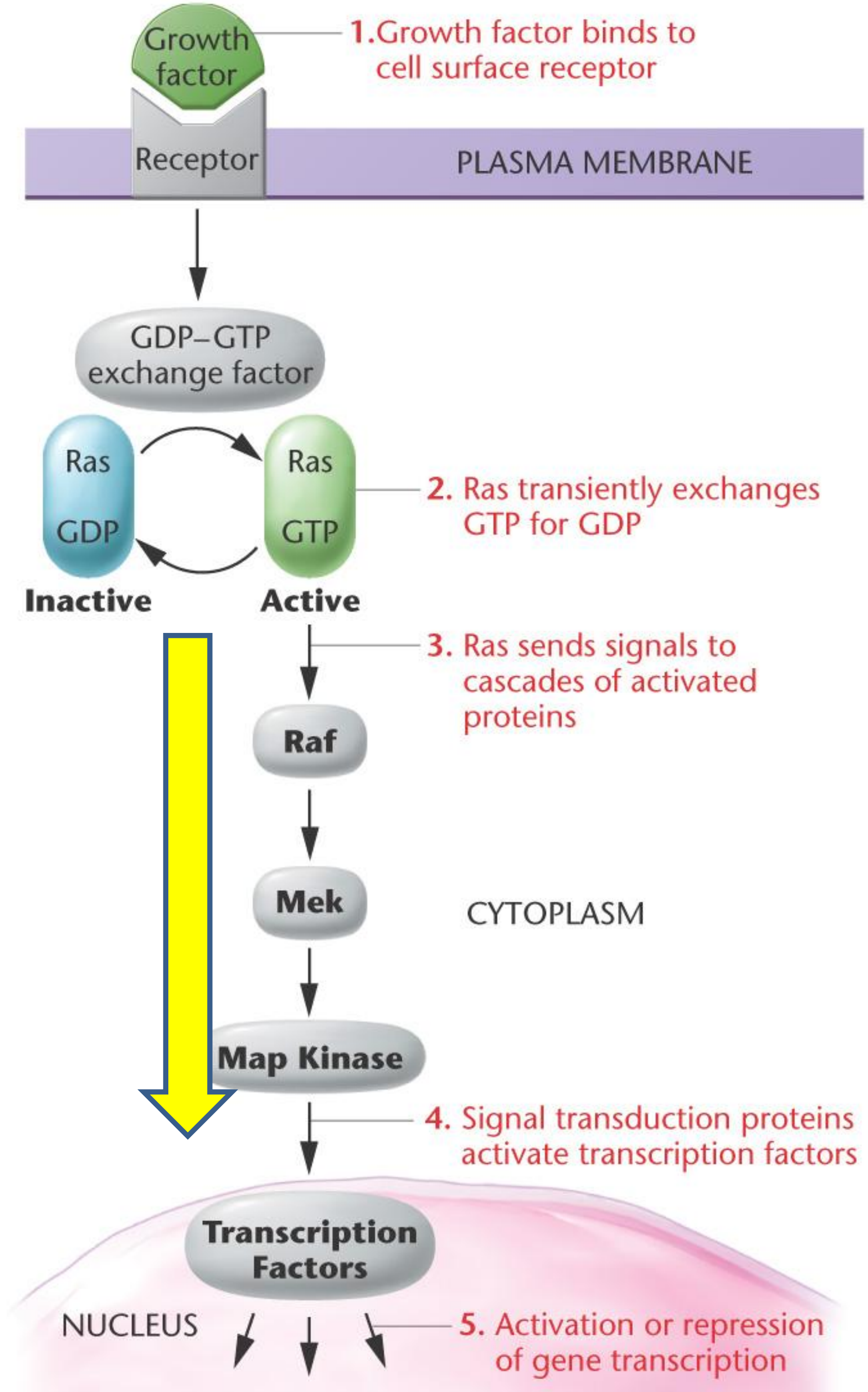
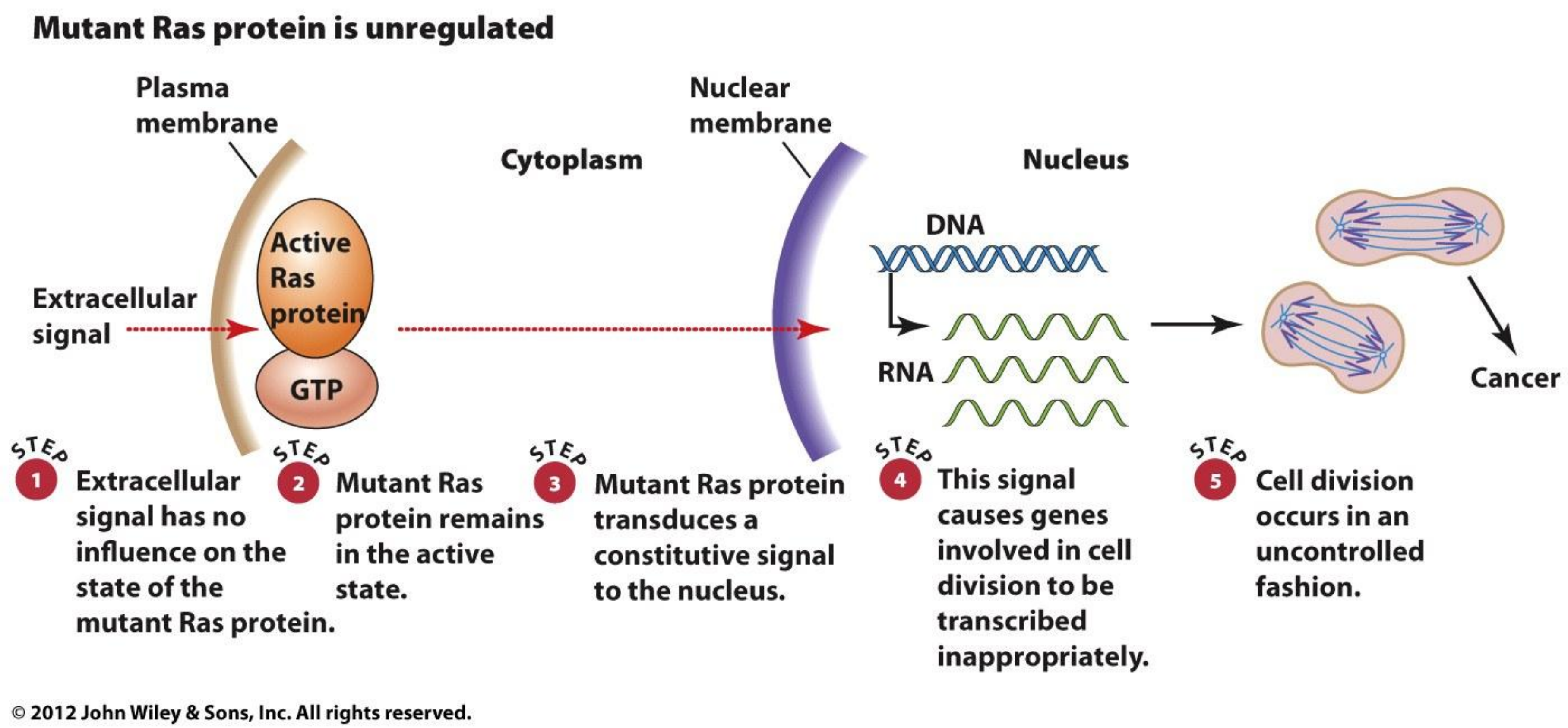
Ras Pathway

- Growth factor binds receptor
- Receptor exchanges GTP for GDP on Ras
  - Ras activated
- Ras→Raf→Mek→Map Kinase→transcription factors→ genes turned on


Growth factor
Receptor
PLASMA MEMBRANE
1.Growth factor binds to cell surface receptor
GDP–GTP exchange factor
Ras
GDP
Ras
GTP
Inactive
Active
2. Ras transiently exchanges GTP for GDP
3. Ras sends signals to cascades of activated proteins
Raf
Mek
CYTOPLASM
Map Kinase
4. Signal transduction proteins activate transcription factors
Transcription Factors
NUCLEUS
5. Activation or repression of gene transcription

Mutant Ras Protein (**V12 or G12V**) is Unregulated



Mutant Ras protein is unregulated

STEP 1 Extracellular signal has no influence on the state of the mutant Ras protein.

STEP 2 Mutant Ras protein remains in the active state.

STEP 3 Mutant Ras protein transduces a constitutive signal to the nucleus.

STEP 4 This signal causes genes involved in cell division to be transcribed inappropriately.

STEP 5 Cell division occurs in an uncontrolled fashion.

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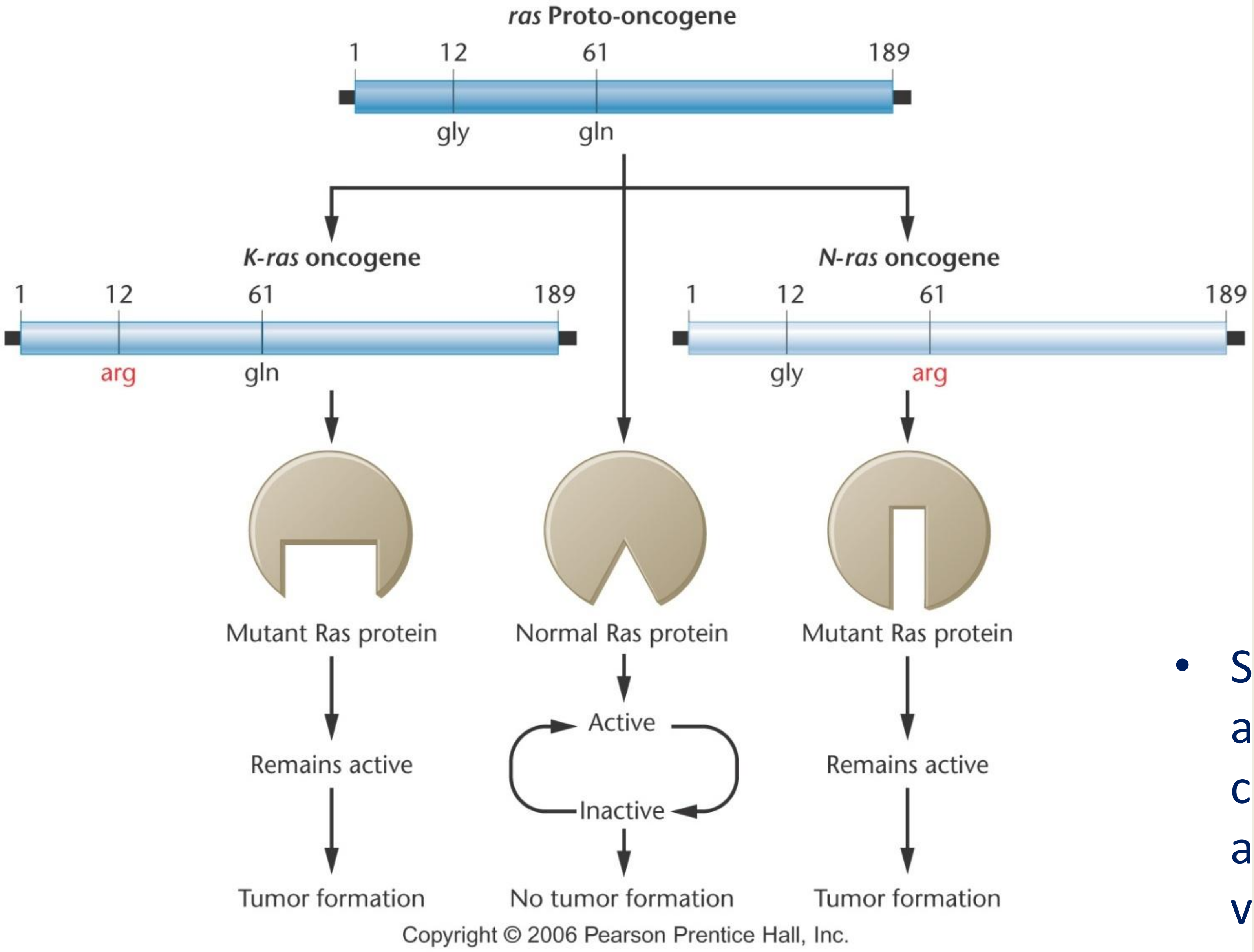
Mutant Ras Protein



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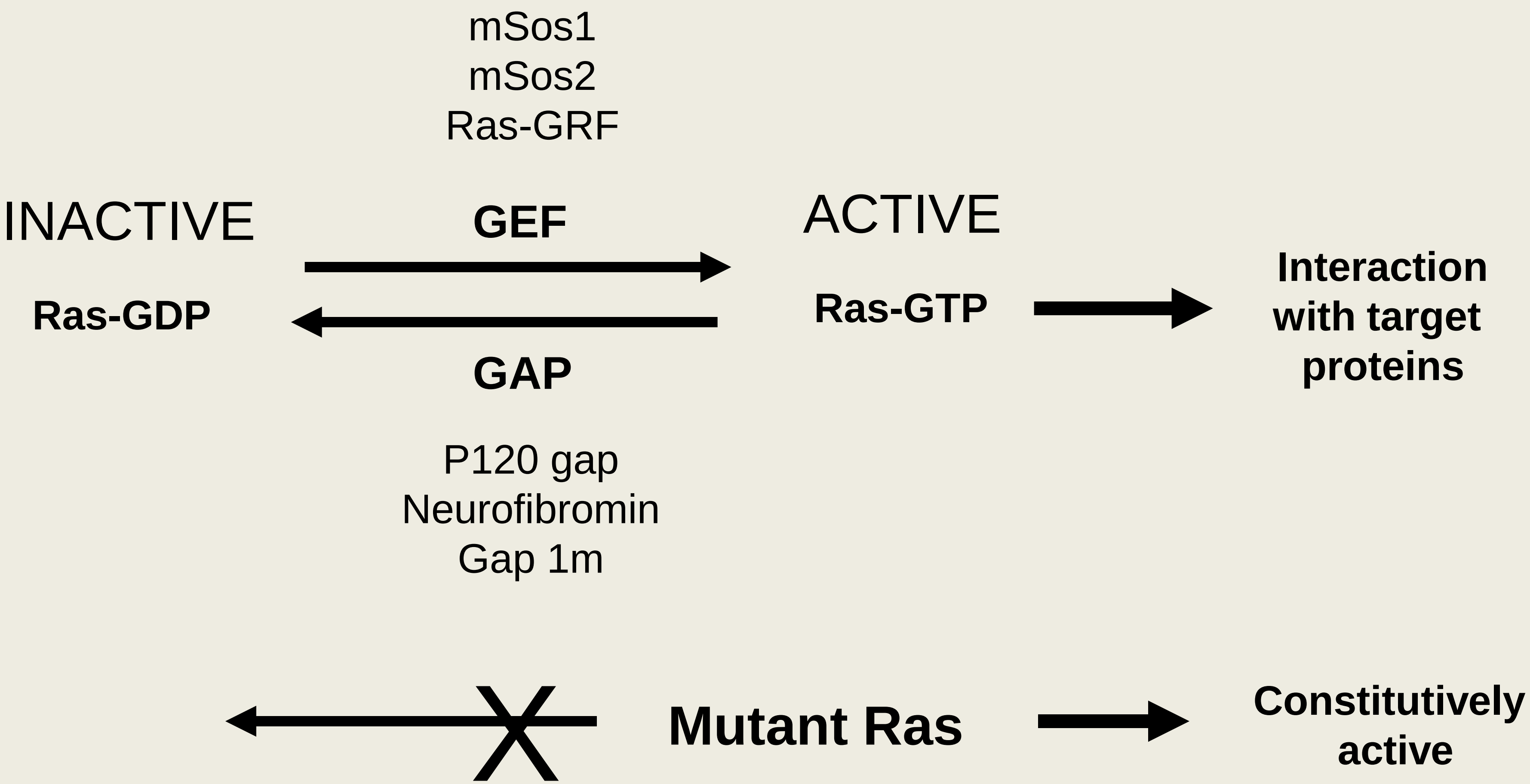
- Single amino acid changes create N-ras and K-ras variants



mSos1
mSos2
Ras-GRF

INACTIVE

Ras-GDP

GEF

GAP

P120 gap
Neurofibromin
Gap 1m

ACTIVE

Ras-GTP

Interaction with target proteins

Mutant Ras

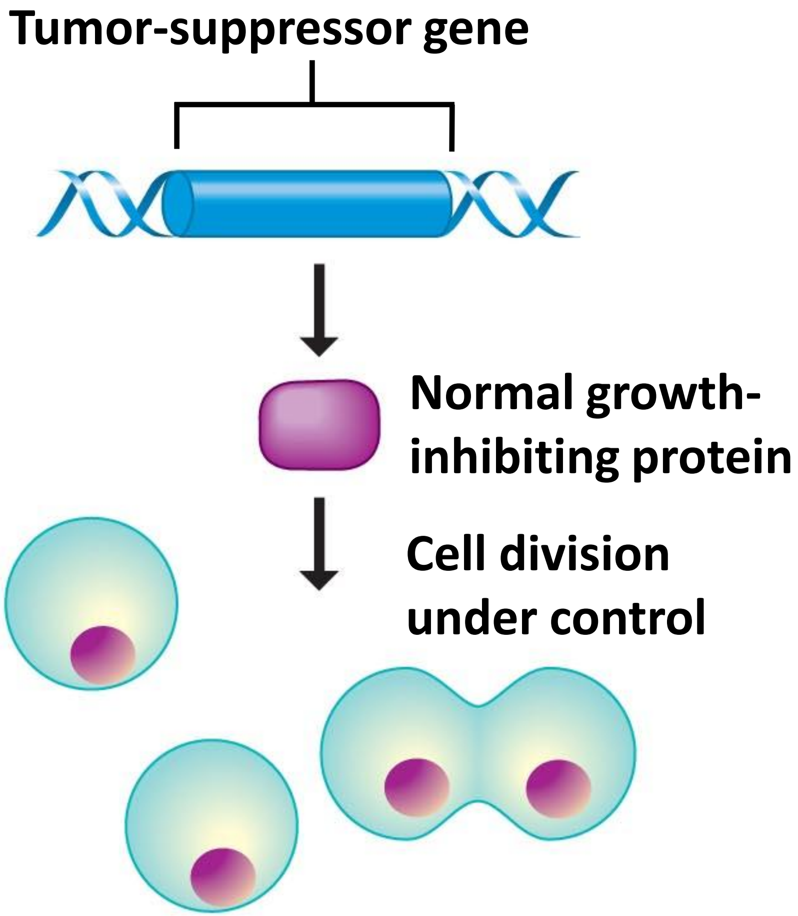
Constitutively active

Tumor-Suppressor Genes

- **Tumor-suppressor genes**
  - Inhibit cell division
  - Prevent uncontrolled cell growth
  - May be mutated and contribute to cancer

- **Tumor-suppressor genes** are at the end of an *inhibitory pathway*; a growth-inhibitory factor can result in turning on a tumor suppressor gene that inhibits the cell cycle.

- The balance between stimulatory and inhibitory signals determines whether proto-oncogenes or tumor-suppressor genes are active, and therefore whether or not cell division occurs.

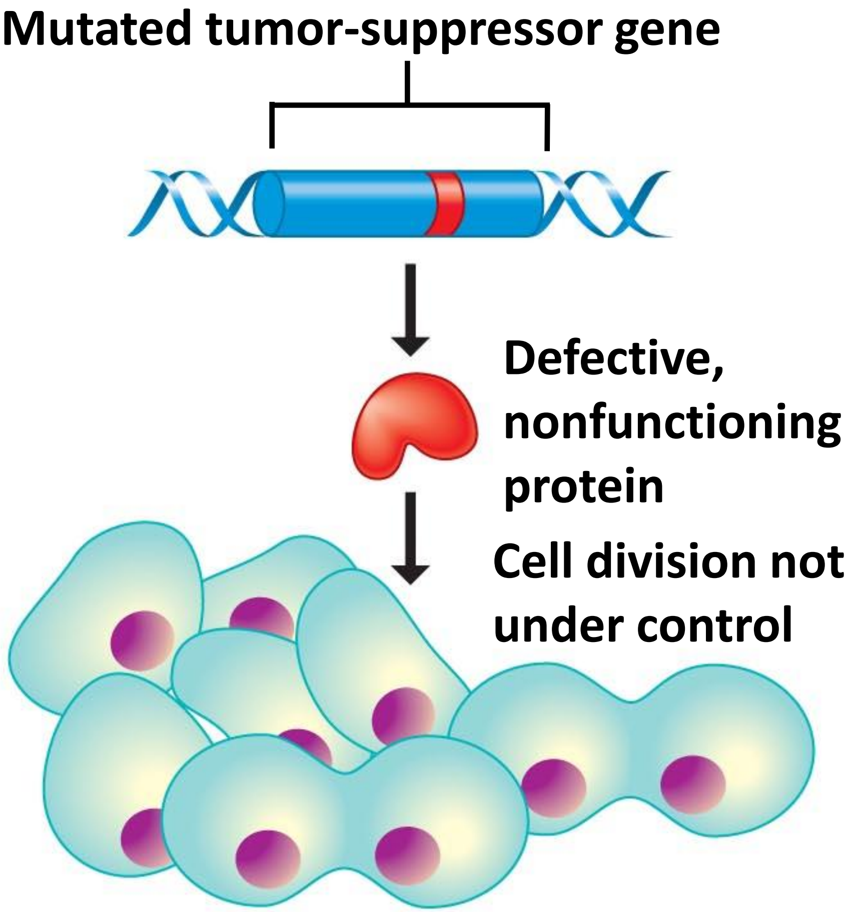


Tumor-suppressor gene

Normal growth-inhibiting protein

Cell division under control

(a) Normal cell growth



Mutated tumor-suppressor gene

Defective, nonfunctioning protein

Cell division not under control

(b) Uncontrolled cell growth (cancer)

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Tumor suppressors

- Normally function to suppress the formation of cancer
  - Growth arrest
  - Apoptosis
  - DNA repair
  - Differentiation
  - Anti-angiogenesis

Tumor Suppressor Genes

Mutations in tumor suppressor genes are usually recessive in their effects on the individual cell.

1. Cell Cycle Regulators:
   - CdkI (cyclin-dependent kinase inhibitors)
   - Rb (Retinoblastoma protein)
   - p53
2. Signaling proteins: APC (adenomatous polyposis coli)
3. DNA damage repair proteins: BRCA1 (Breast cancer gene)
4. Enzymes: PTEN (phosphatase and tensin homolog deleted in chromosome ten)

RB1 Tumor Suppressor Gene

- Retinoblastoma 1 gene
- Involved in breast, bone, lung, bladder and retinal cancers (among others)
- Inheriting one mutated (inactivated) copy of gene increases chances of retinoblastoma formation from 1/14,000-20,000 to 85% (plus increases other cancer rates)
  - Loss of second copy in a cell eliminates function
  - Normal cells unlikely to lose both good copies

pRB Function

- Tumor suppressor protein that controls the G1/S checkpoint
- Found in nucleus and activity regulated by level of phosphorylation (by CDK4/cyclinD1 complex)
  - Nonphosphorylated version binds to TFs such as E2F, inactivating them
  - Free E2F and the other regulators turn on >30 genes required for transition to S phase

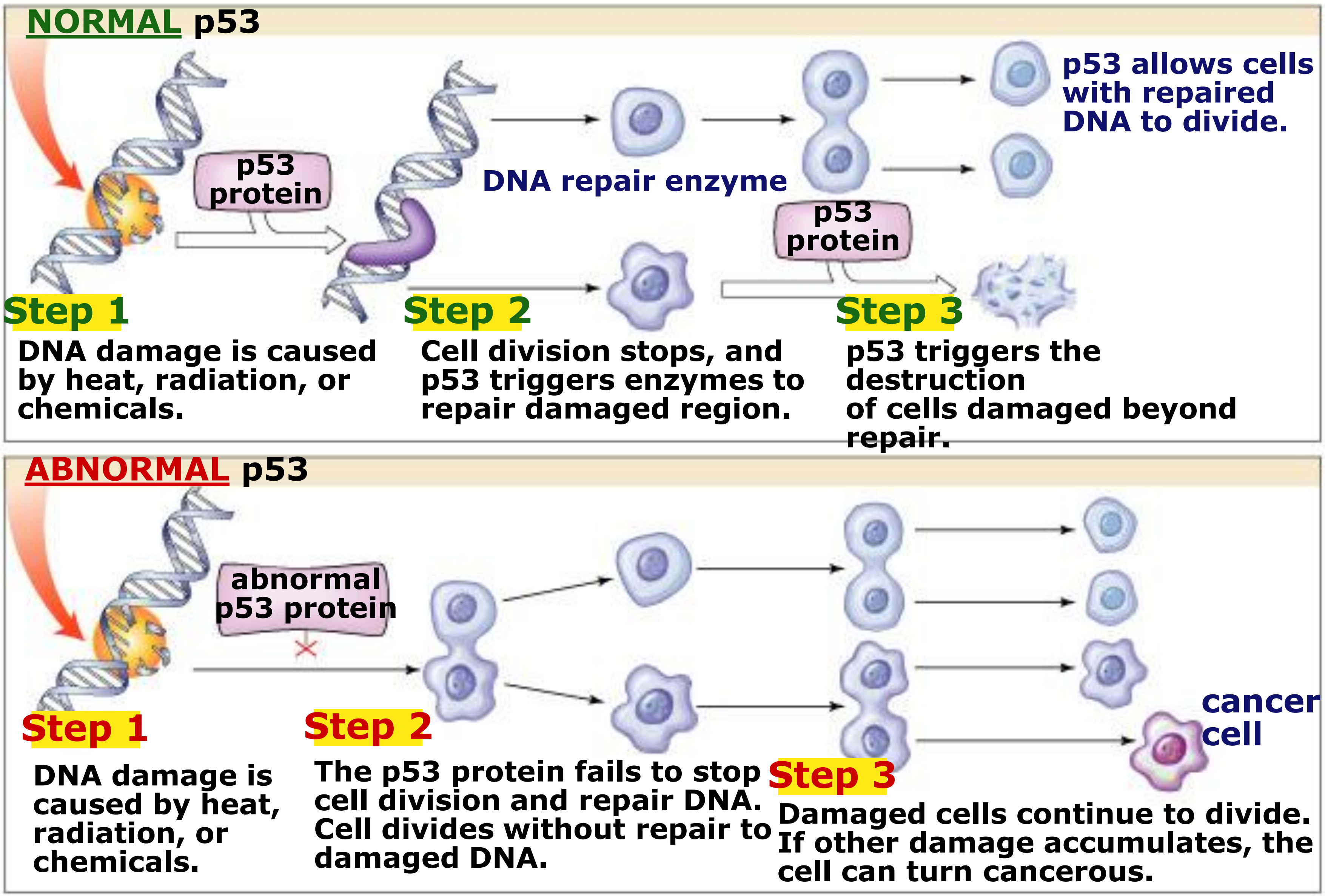
p53 Tumor Suppressor Gene

- Mutated (inactivated) in more than 50% of all cancers
- p53 regulates (activates or represses) transcription of more than 50 different genes
- p53 regulated by Mdm2 (prevents the phosphorylations and acetylations that activate inactive p53)
- Activated p53 levels rise rapidly if DNA is damaged or repair intermediates accumulate

P53 Function

- Activated p53 acts as transcription factor to turn on genes that
  - arrest the cell cycle so DNA can be repaired
    - Initiates synthesis of p21, which inhibits CDK4/cyuclinD1 complex, blocking entry into S phase
    - Genes expressed which retard rate of DNA replication
    - Other products block G2/M progression
  - Initiate apoptosis if DNA cannot be readily repaired
    - Turns on *Bax* gene, represses *Bcl2* gene
    - Bax homodimers activate process of cell destruction
    - Cancer cells lacking p53 do not initiate pathway even if DNA/cellular damage is great

p53 — master regulator gene



NORMAL p53

p53 protein

DNA repair enzyme

p53 allows cells with repaired DNA to divide.

p53 protein

Step 1

DNA damage is caused by heat, radiation, or chemicals.

Step 2

Cell division stops, and p53 triggers enzymes to repair damaged region.

Step 3

p53 triggers the destruction of cells damaged beyond repair.

ABNORMAL p53

abnormal p53 protein

cancer cell

Step 1

DNA damage is caused by heat, radiation, or chemicals.

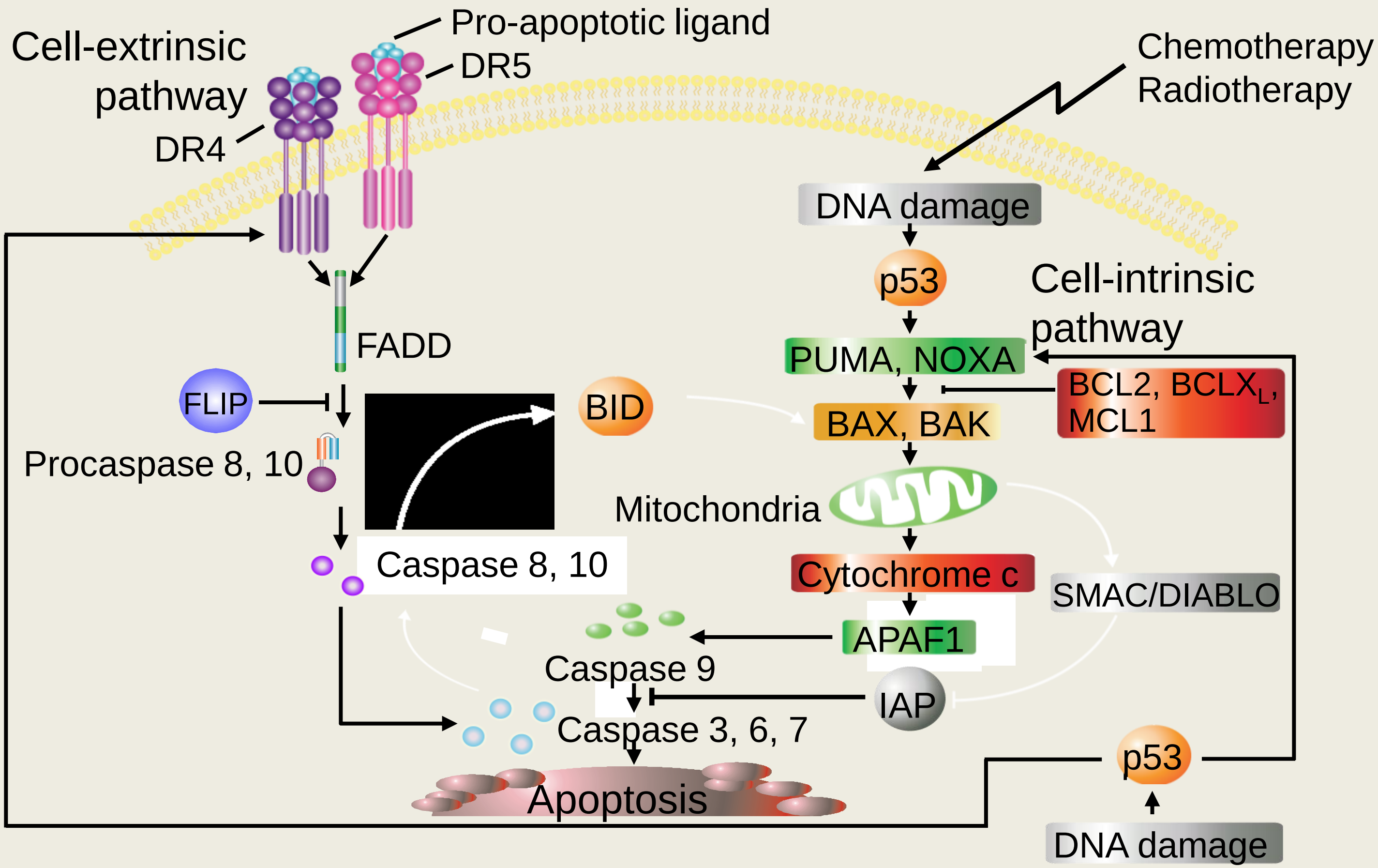
Step 2

The p53 protein fails to stop cell division and repair DNA. Cell divides without repair to damaged DNA.

Step 3

Damaged cells continue to divide. If other damage accumulates, the cell can turn cancerous.

Activated Caspase 3, 6, and 7 Execute Apoptosis in Tumor Cells



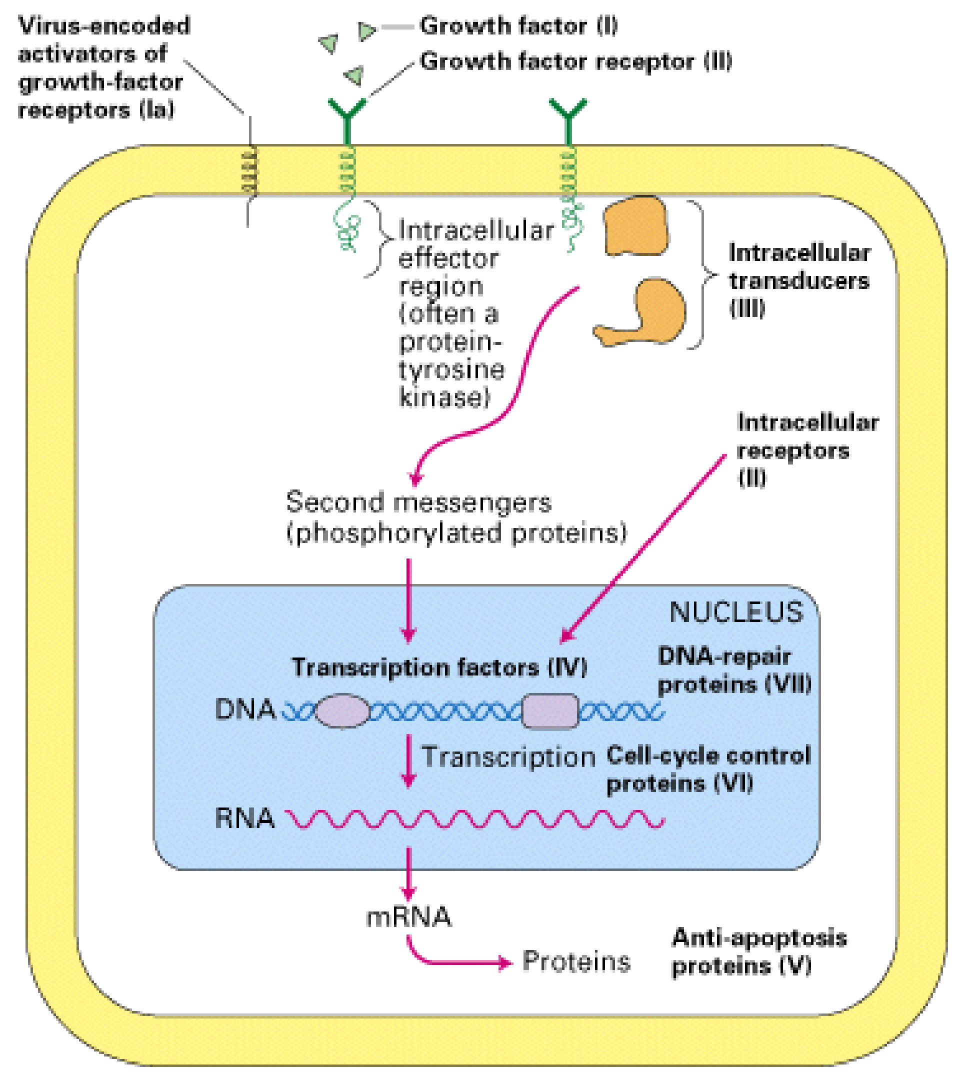
Comparison of Proto-oncogenes and tumor suppressors

Property	**Tumor suppressor genes**	**Proto-oncogenes**
Alleles mutated in cancer	Both alleles	One allele
Germ line transmission of mutant allele	frequent	Rare (1 example)
Somatic mutations	yes	yes
Function of mutant allele	Loss of function (recessive allele)	Gain of function (dominant allele)
Effects on cell growth	Inhibit cell growth	Promote cell growth

Tumor suppressors are *recessive* –
require mutation of both alleles

Oncogenes are *dominant* –
mutation of 1 allele is sufficient

Proteins that control cell growth


Virus-encoded activators of growth-factor receptors (Ia)
Growth factor (I)
Growth factor receptor (II)
Intracellular effector region (often a protein-tyrosine kinase)
Intracellular transducers (III)
Intracellular receptors (II)
Second messengers (phosphorylated proteins)
NUCLEUS
Transcription factors (IV)
DNA-repair proteins (VII)
DNA
Transcription
Cell-cycle control proteins (VI)
RNA
mRNA
Proteins
Anti-apoptosis proteins (V)

1. Growth factors and receptors: (EGF/EGFR, IGF/IGFR, PDGF/PDGFR)

2. Intracellular transducers:

GTP binding proteins: Ras

Protein kinases: Src, Raf

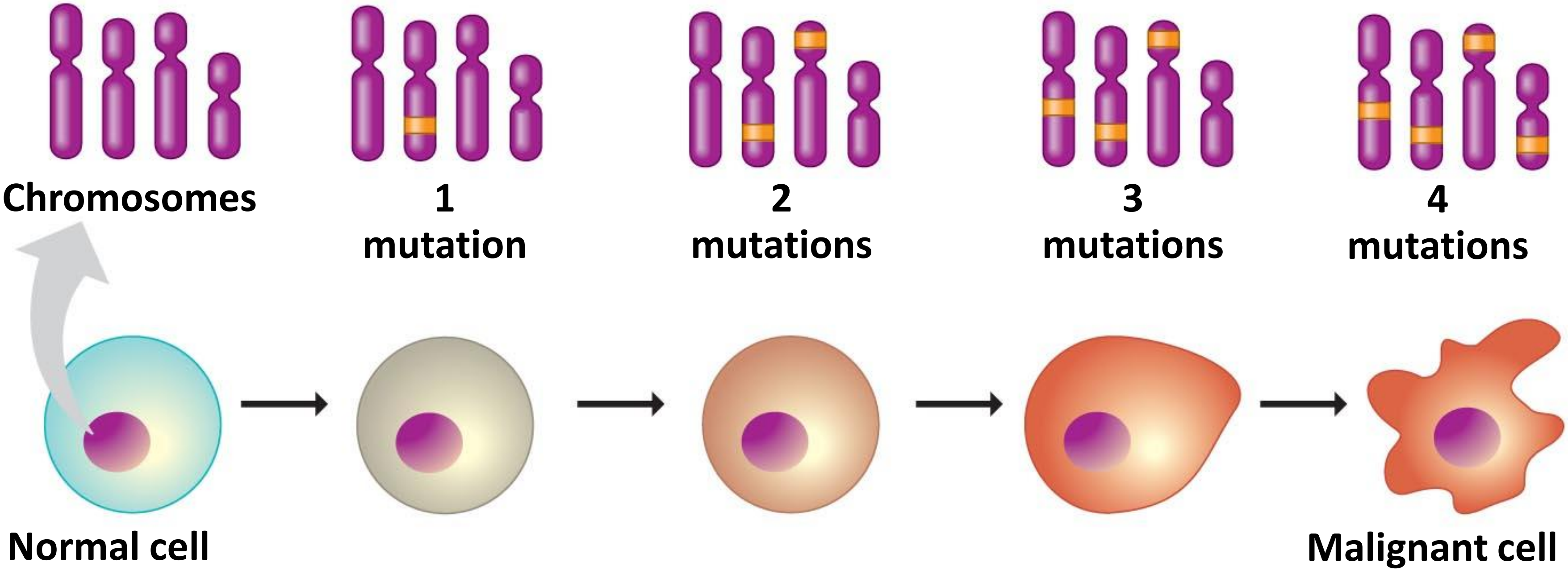
3. Intracellular receptors: ER, RAR

4. DNA repair proteins: BRCA1

5. Cell cycle control proteins: cyclins, cdkis, Rb, p53

6. Transcription factors: myc, jun. fos, myb

7. Anti apoptotic proteins: Akt, Bcl-2



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Transforming Viruses

- Viruses discovered to cause cancer in animals
  - Acute transforming viruses
    - Commonly but not always retroviruses
  - Rous sarcoma virus (RSV) discovered by Francis Peyton Rous discovered in 1910 as a causative agent of chicken sarcomas (solid tumors of muscle, bone or fat)
    - Many years later shown to be retrovirus
    - Nobel Prize in 1966 (link of viruses to cancer)

Oncogenic viruses and cancer

Family	**Associated Cancer(s)**
RNA viruses	
Flaviriridae	
Hepatitis C virus	**Hepatocellular carcinoma**
Retroviridae	**Haemopoetic cancers, sarcomas, carcinomas**
DNA viruses	
Adenoviridae	**Various solid tumors**
Hepadnaviridae	**Hepatocellular carcinoma**
Herpesviridae	**Lymphomas, carcinomas, sarcomas**
Papillomaviridae	**Papillomas and carcinomas**
Polyomaviridae	**Various solid tumors**
Poxviridae	**Myxomas and fibromas**

Tumor-Inducing Retroviruses and Viral Oncogenes

- Retroviruses have an **RNA** genome.
- The **Rous sarcoma virus**, the first tumor-inducing virus, contains four genes
  - *gag* encodes the capsid protein of the virus
  - *pol* encodes the reverse transcriptase
  - *env* encodes a viral envelope protein
  - ***v-src*** encodes a protein kinase that inserts into the plasma membranes of infected cells. The *v-src* gene is an oncogene that is responsible for the virus's ability to **induce abnormal cell growth**.

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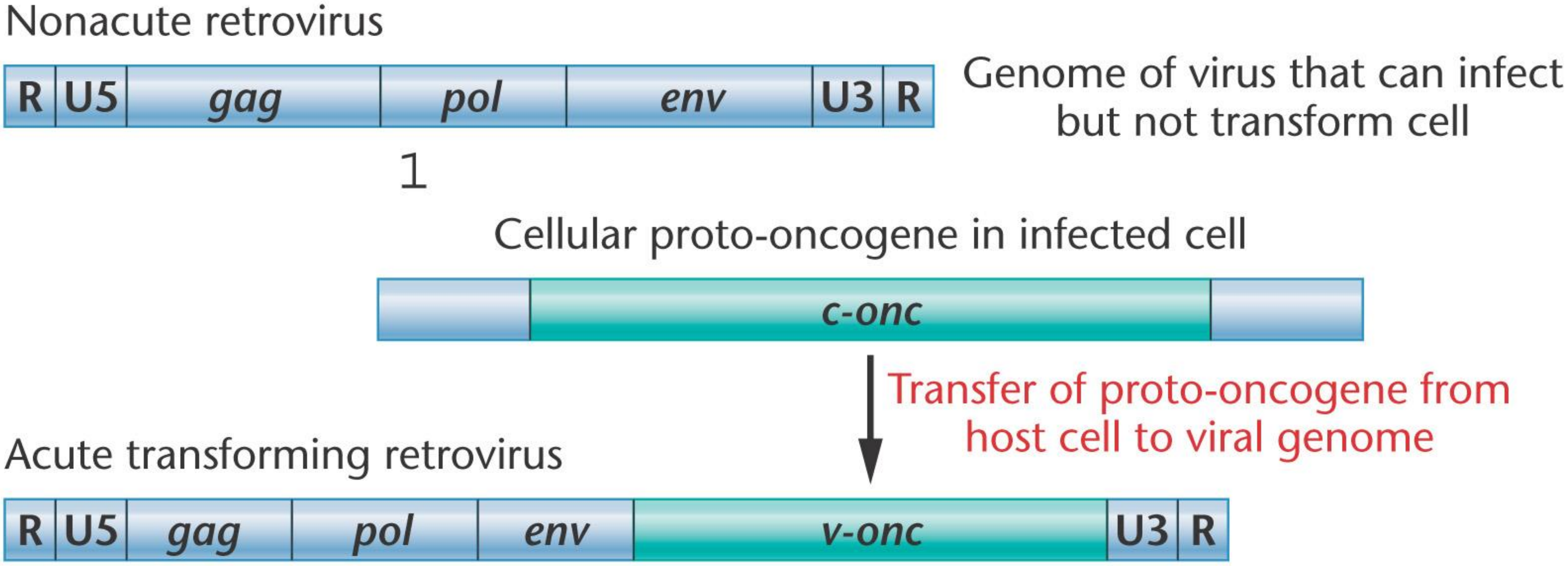
Retroviruses

- ssRNA chromosome
- Chromosome copied to DNA by reverse transcriptase upon entry into cell
- DNA integrated into host cell chromosome
  - Provirus
- Provirus has strong promoter elements in U5 and U3 terminal sequences
  - U5 expresses *gag*, *pol* and *env*
- Oncogenic when
  - Integrate near proto-oncogene and cause inappropriate or over expression
  - Bring v-onc as part of viral chromosome

Retroviruses



Nonacute retrovirus

Genome of virus that can infect but not transform cell

Cellular proto-oncogene in infected cell

Transfer of proto-oncogene from host cell to viral genome

Acute transforming retrovirus

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- Many transforming retroviruses are defective in the sense that one or more of *gal/pol/env* have been deleted to make room for the v-onc

Viral Oncogenes

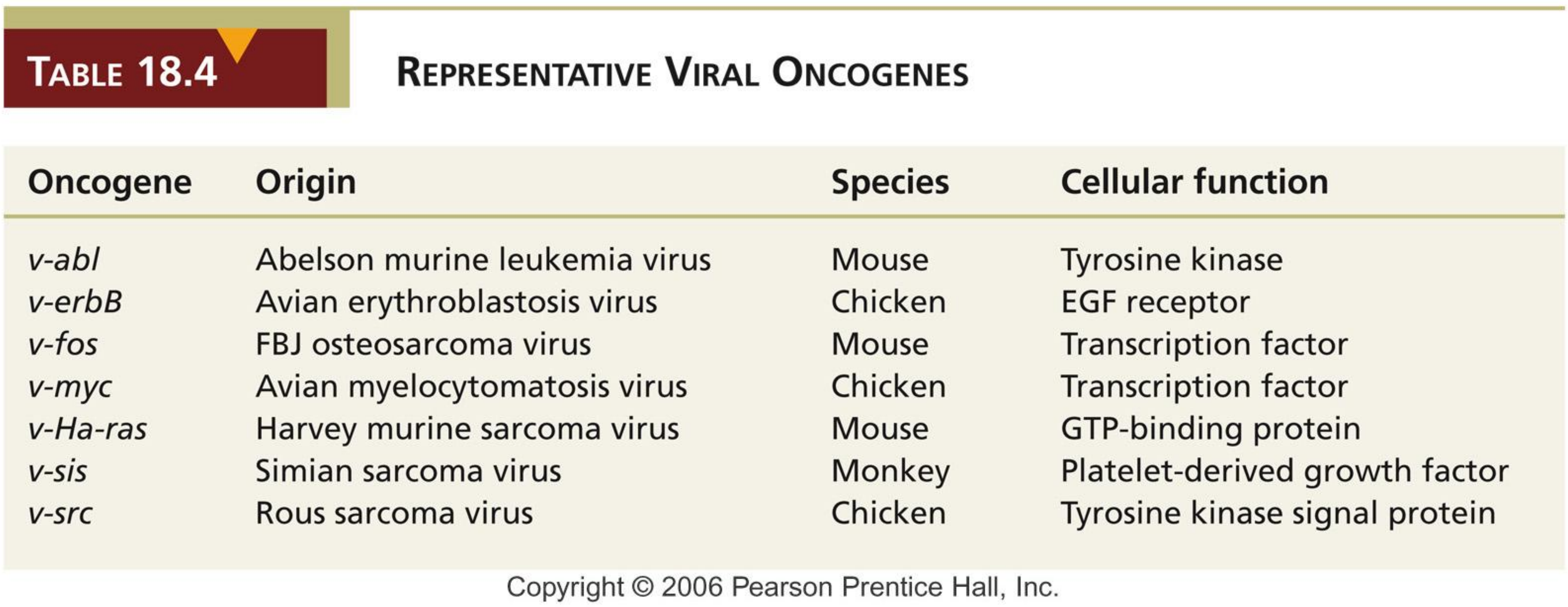

TABLE 18.4 REPRESENTATIVE VIRAL ONCOGENES

Oncogene	Origin	Species	Cellular function
v-abl	Abelson murine leukemia virus	Mouse	Tyrosine kinase
v-erbB	Avian erythroblastosis virus	Chicken	EGF receptor
v-fos	FBJ osteosarcoma virus	Mouse	Transcription factor
v-myc	Avian myelocytomatosis virus	Chicken	Transcription factor
v-Ha-ras	Harvey murine sarcoma virus	Mouse	GTP-binding protein
v-sis	Simian sarcoma virus	Monkey	Platelet-derived growth factor
v-src	Rous sarcoma virus	Chicken	Tyrosine kinase signal protein

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- Most *v-onc* genes have normal cellular counterparts
  - If simply mutated to the oncogenic form and not in a virus are called *c-onc*

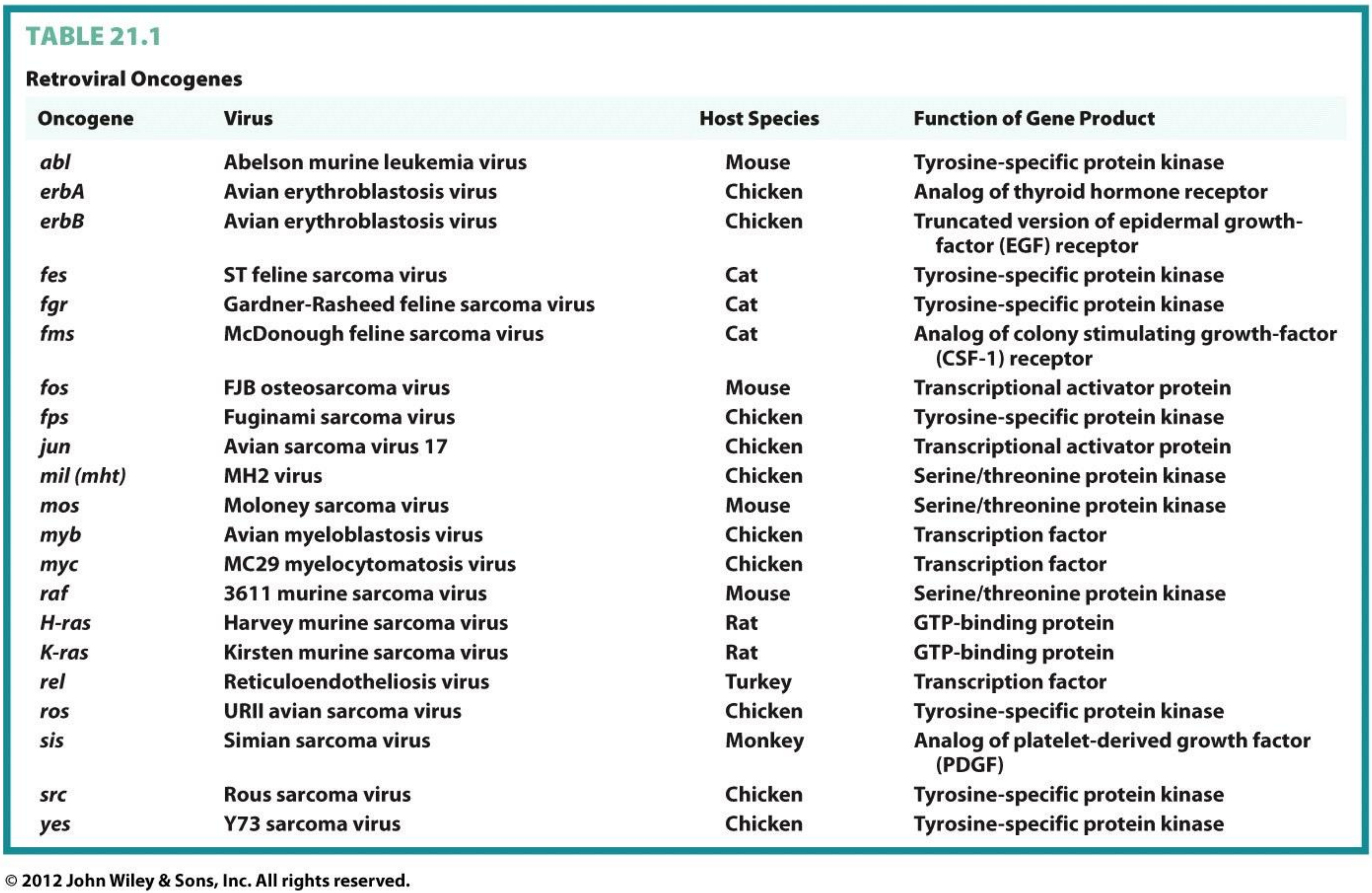

TABLE 21.1

Retroviral Oncogenes

Oncogene	Virus	Host Species	Function of Gene Product
abl	Abelson murine leukemia virus	Mouse	Tyrosine-specific protein kinase
erbA	Avian erythroblastosis virus	Chicken	Analog of thyroid hormone receptor
erbB	Avian erythroblastosis virus	Chicken	Truncated version of epidermal growth-factor (EGF) receptor
fes	ST feline sarcoma virus	Cat	Tyrosine-specific protein kinase
fgr	Gardner-Rasheed feline sarcoma virus	Cat	Tyrosine-specific protein kinase
fms	McDonough feline sarcoma virus	Cat	Analog of colony stimulating growth-factor (CSF-1) receptor
fos	FJB osteosarcoma virus	Mouse	Transcriptional activator protein
fps	Fuginami sarcoma virus	Chicken	Tyrosine-specific protein kinase
jun	Avian sarcoma virus 17	Chicken	Transcriptional activator protein
mil (mht)	MH2 virus	Chicken	Serine/threonine protein kinase
mos	Moloney sarcoma virus	Mouse	Serine/threonine protein kinase
myb	Avian myeloblastosis virus	Chicken	Transcription factor
myc	MC29 myelocytomatosis virus	Chicken	Transcription factor
raf	3611 murine sarcoma virus	Mouse	Serine/threonine protein kinase
H-ras	Harvey murine sarcoma virus	Rat	GTP-binding protein
K-ras	Kirsten murine sarcoma virus	Rat	GTP-binding protein
rel	Reticuloendotheliosis virus	Turkey	Transcription factor
ros	URII avian sarcoma virus	Chicken	Tyrosine-specific protein kinase
sis	Simian sarcoma virus	Monkey	Analog of platelet-derived growth factor (PDGF)
src	Rous sarcoma virus	Chicken	Tyrosine-specific protein kinase
yes	Y73 sarcoma virus	Chicken	Tyrosine-specific protein kinase

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Proteins Encoded by Viral Oncogenes

- *Growth factors* similar to those encoded by cellular genes
- Proteins similar to growth-factor and hormone *receptors*
- *Tyrosine kinases* that do not span the plasma membrane
- *Transcription factors* homologous to cellular proteins
- ***Any protein***

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Human Cancer-Associated Viruses

- To date no acute transforming retroviruses have been discovered in humans
  - Viruses can contribute to but not be the sole cause of human cancer
  - However, up to 15% of all cancers have a *viral association*
    - Papillomaviruses HPV 16 and 18, hepatitis B virus, Epstein-Barr virus, Human T-cell leukemia virus are examples of cancer-associated viruses

Human Viruses Associated With Cancer

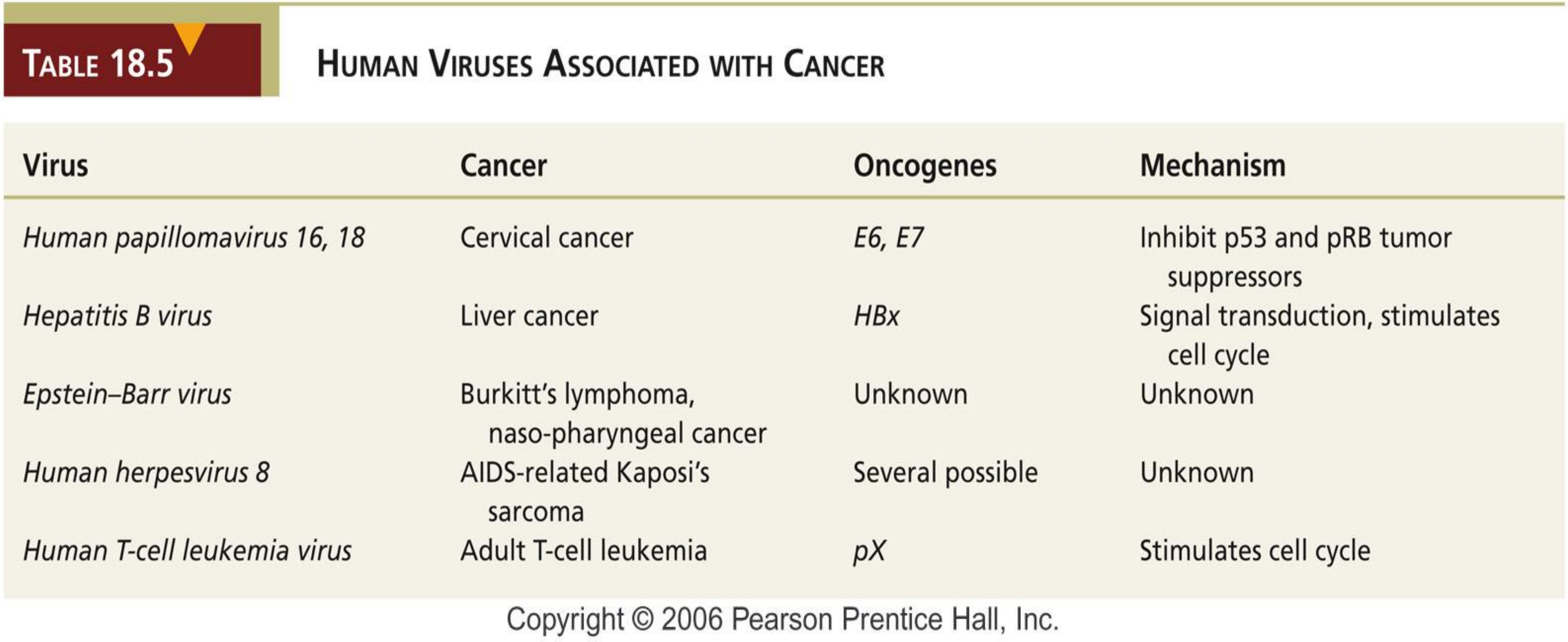

TABLE 18.5 HUMAN VIRUSES ASSOCIATED WITH CANCER

Virus	Cancer	Oncogenes	Mechanism
Human papillomavirus 16, 18	Cervical cancer	*E6, E7*	Inhibit p53 and pRB tumor suppressors
Hepatitis B virus	Liver cancer	*HBx*	Signal transduction, stimulates cell cycle
Epstein–Barr virus	Burkitt's lymphoma, naso-pharyngeal cancer	Unknown	Unknown
Human herpesvirus 8	AIDS-related Kaposi's sarcoma	Several possible	Unknown
Human T-cell leukemia virus	Adult T-cell leukemia	*pX*	Stimulates cell cycle

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- Non-retroviral varieties
- Many of these *v-onc* genes act to stimulate the cell cycle (viruses needs host replication apparatus to multiply)

V-onc Gene Product Action

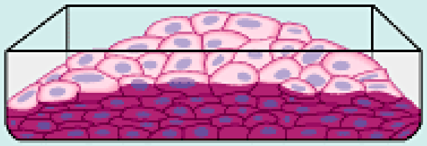
- Some *v-onc* gene products have their transforming effect by binding and thereby *“taking out” certain tumor suppressor gene* products
  - Cell division required to provide replication apparatus for virus
  - Bad, but does open some interesting treatment possibilities…

Tumors

- Mass of abnormal cells
  - Benign tumor
    - abnormal cells remain at original site as a lump
      - p53 has halted cell divisions
    - most do not cause serious problems & can be removed by surgery
  - Malignant tumors
    - cells leave original site
      - lose attachment to nearby cells
      - carried by blood & lymph system to other tissues
      - start more tumors = metastasis
    - impair functions of organs throughout body

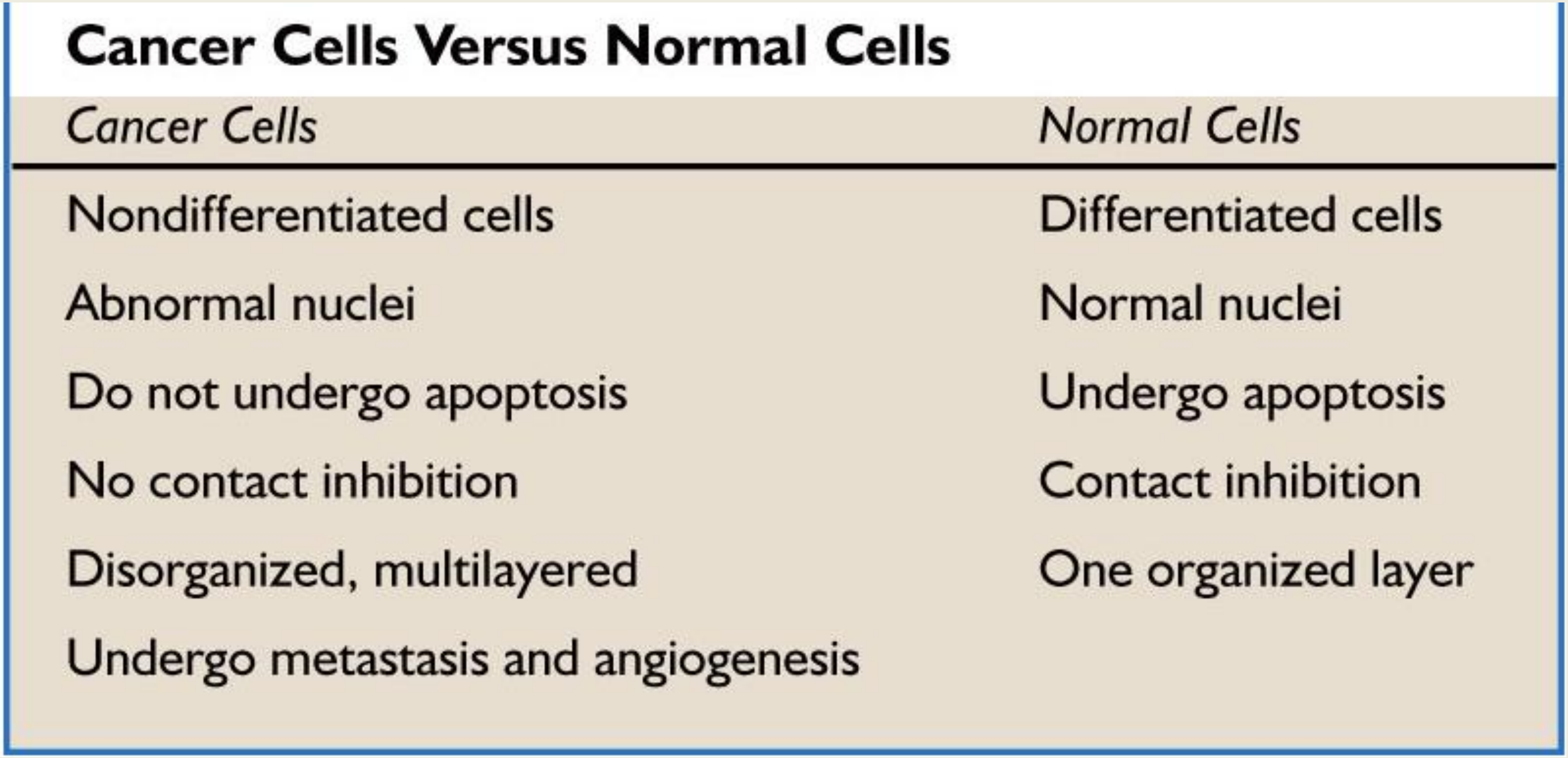
Development of Cancer

- Cancer develops only after a cell experiences ~6 key mutations (“hits”)
  - unlimited growth
    - turn on growth promoter genes
  - ignore checkpoints
    - turn off tumor suppressor genes (p53)
  - escape apoptosis
    - turn off suicide genes
  - immortality = unlimited divisions
    - turn on chromosome maintenance genes
  - promotes blood vessel growth
    - turn on blood vessel growth genes
  - overcome anchor & density dependence
    - turn off touch-sensor gene



(b) Cancer cells

Cancer cells do not exhibit anchorage dependence or density-dependent inhibition.



Cancer Cells Versus Normal Cells

Cancer Cells	*Normal Cells*
Nondifferentiated cells	Differentiated cells
Abnormal nuclei	Normal nuclei
Do not undergo apoptosis	Undergo apoptosis
No contact inhibition	Contact inhibition
Disorganized, multilayered	One organized layer
Undergo metastasis and angiogenesis	